Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

SOLICITUD PCT

PATENTE DE INVENCIÓN

21 **EXPEDIENTE No.** 05-102555.

54 **TÍTULO** ACIDOS CARBOXILICOS ALFA SUSTITUIDOS COMO MODULADORES PPAR

51 **CLASIFICACIÓN INTERNACIONAL** A61K31/42 ; A61K31/44

71 **SOLICITANTE** PFIZER INC.

DOMICILIO 235 East 42nd Street, New York, NY 10017, EU A

74 **APODERADO** CARLOS M. OLARTE

22 **BOGOTÁ, D. C.,** Octubre 7 de 2005

(FORMA P-10)

OLARTERAISBECK 05/134.

Industria y Comercio
SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO
Radicacion : 05106655 00000000 Folios: 402
Fecha (AMD): 2005-10-07 16:58:40
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL

SOLICITUD DE:

(1)

[X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[ ] Capítulo I. [X] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: PFIZER INC
Dirección: 235 East 42nd Street, New York, NY 10017 E.U.A.
Nacionalidad o Domicilio: ESTADOUNIDENSE
Lugar de Constitución: Delaware, Estados Unidos de América.
Teléfono: _____ **Fax:** _____
E-mail: _____

IDENTIFICACIÓN
C.C. [ ] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual _____
Número _____

REPRESENTANTE O APODERADO

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

IDENTIFICACIÓN
C.C. [X] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual _____
Número 79.782.747Bta
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/IB2004/001159 Fecha Abril 1, 2004

Publicación Internacional No. WO 2004/092145 Fecha Octubre 28, 2004

(6) **Título (54)** **ACIDOS CARBOXILICOS ALFA SUSTITUIDOS COMO MODULADORES PPAR.**

A61K31/42, A61K31/44

Clasificación Internacional (51) C07D 263/32, C07C 59/125, C07D 401/04, 411/12, 249/06, 213/66, C07C 61/04, C07D 307/79, 413/14, 417/14, 405/06, 413/12

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

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Abril 15, 2003	60/463,213

(9) **Comprobante de pago No.** 77,061 **Fecha** Octubre 6, 2005

(10) ANEXOS

- [x] 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.
- [x] Poderes, si fuere el caso.
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [x] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(11) FIGURA CARACTERÍSTICA:

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

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

LISTA DE INVENTORES PCT/IB2004/001159

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Estados Unidos de América
Nacionalidad: Estadounidense

4

SUPERINDUSTRIA Y COMERCIO
Radicacion : 05182555 00000000 Folios: 462
Fecha (AMD): 2005-10-07 16:58:48
Tramite : 611 PCI-PATENT 379 FASE NALI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 05 - 77,061
FECHA : OCTUBRE 6 DE 2005

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEGR	CONSIGNACION	BANCO POPULAR	050-00110-6	41777111	05/10/2005	3,010,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	443,000.00
		TOTAL : $	443,000.00

SON: CUATROCIENTOS CUARENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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

APOSTILLA EN PODER DE REPRESENTACIÓN DE

PFIZER INC.

Bilingüe inglés- español otorgado en Nueva York, Estados Unidos el 14 de julio de 2003 y firmado por J. Trevor Lumb, Vicepresidente de Pfizer Products Inc.

CERTIFICACION NOTARIAL

Bilingüe inglés- español, el 14 de julio de 2003 el suscrito notario Kenneth Greenwood certifica que J. Trevor Lumb, domiciliado en Nueva York ejercía funciones de Asistente General Consejero de Patentes la Compañía Pfizer Inc., con sede en Nueva York, Nueva York, Estados Unidos.

Firma del notario: Kenneth Greenwood

Sello notarial: certificado, verificado y autenticado en la Localidad de Egham en Surrey, 14 julio, 2003 por el Notario Kenneth Greenwood-Horne Engall & Freeman Sello Notario Público en alto relieve rojo.

APOSTILLA

REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE

1. País :Reino Unido de Gran Bretaña e Irlanda del Norte
   Este documento Público
2. ha sido firmado por K. Greenwood
3. ejerce funciones de Notario Público
4. Lleva el sello de dicho Notario Público

CERTIFICADÓ

5. En Londres 6. El 17 de julio de 2003
7. Por el Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la mancomunidad
8. No. G210434
9. Sello del Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la mancomunidad
10. Firma de R. Bawden - Por Secretario de Estado

Si el documento se usa en un país que no es parte de la convención de la Haya del 5 de octubre 1961, debe presentarse en sección consular de la misión que representa el país.

Es traducción fiel del inglés, con copia archivo para confrontación. Bogotá 25 de julio-2003. Marlen Neira C

MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Inglés - Español - Inglés
Resolución No. 2117 del 7 Oct 1997

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

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

www.olarteraisbeck.com

Power of Attorney

The undersigned,

Pfizer Inc.

domiciled in

235 East 42nd Street, New York, NY 10017 USA

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

Poder

El suscrito,

Pfizer Inc.

domiciliado en

235 East 42nd Street, New York, NY 10017 USA

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

Signature/Firma: _____

Date/Fecha: July 14, 2003

City,Country/Ciudad,País: New York, USA

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

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Notarial Certification

On this date,
July 14, 2003
The undersigned Notary Public certifies:

1. That J. Trevor Lumb
of legal age and domiciled in New York, USA
signed the foregoing document.

2. That the grantor has executed the foregoing document as Assistant General Patent Counsel of Pfizer Inc.

3. That Pfizer Inc.,
having its principal place of business located in New York, New York, U.S.A.
is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

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

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

NOTARY PUBLIC (Signature):

EXECUTION
Certified Verified and Authenticated
In The Town Of Egham In Surrey
This 14th Day Of July 2003

KENNETH GREENWOOD
NOTARY PUBLIC
HORNE ENGLAND AND FREEMAN

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que
J. Trevor Lumb
mayor de edad y domiciliado
New York
suscribió el documento que antecede.

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

4. Que
con sede principal ubicada en

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

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

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

26 SEP 2003
María Eugenia Rojas de Urueta
NOTARIA VEINTIOCHO

APOSTILLE
(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
   Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

   This public document / Le présent acte public

2. Has been signed by — K Greenwood
   a été signé par

3. Acting in the capacity of — Notary Public
   agissant en qualité de

4. Bears the seal/stamp of — The Said Notary Public
   est revêtu du sceau/timbre de

5. at London/à Londres — Certified/Attesté

6. the/le — 17 July 2003

7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
   par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/sous No — G210434

9. Stamp:
   timbre:

10. Signature: R. Bawden

FOREIGN AND COMMONWEALTH OFFICE LONDON

For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961,
it should be presented to the consular section of the mission representing that country.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

REVISED VERSION

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 October 2004 (28.10.2004)

PCT

(10) International Publication Number
WO 2004/092145 A1

(51) International Patent Classification[7]: C07D 263/32, C07C 59/125, C07D 401/04, 411/12, 249/06, 213/66, C07C 61/04, C07D 307/79, 413/14, 417/14, 405/06, 413/12

(21) International Application Number: PCT/IB2004/001159

(22) International Filing Date: 1 April 2004 (01.04.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/463,213 15 April 2003 (15.04.2003) US

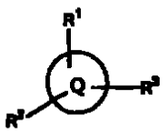
(71) Applicant (*for all designated States except US*): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): BAILEY, Simon [GB/US]; Pfizer Global Research and Development, La Jolla Laboratoires, 10770, Science Center Drive, San Diego, CA 92121 (US). HUMPHRIES, Paul, Stuart [GB/US]; Pfizer Global Research and Development, La Jolla Laboratoires, 10770, Science Center Drive, San Diego, CA 92121 (US). SKALITZKY, Donald, James [US/US]; Pfizer Global Research and Development, 2800 Plymouth Road, Ann Arbor, MI 48105 (US). SU, Wei-Guo [US/US]; Pfizer Global Research and Development, La Jolla Laboratoires, 10770, Science Center Drive, San Diego, CA 92121. ZEHNDER, Luke, Raymond [US/US]; Pfizer Global Research and Development, La Jolla Laboratoires, 10770, Science Center Drive, San Diego, CA 92121.

[Continued on next page]

(54) Title: ALPHA SUBSTITUTED CARBOXYLIC ACID AS PPAR MODULATORS



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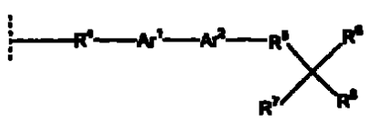

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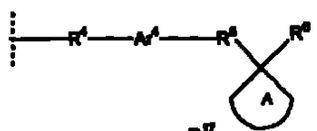
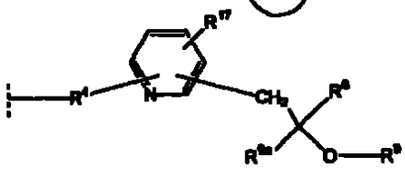
(III)



(IV)



(V)

(57) Abstract: Alpha substituted carboxylic acids of formula (I): wherein R' and R2 are as defined in the specification and R3 is A) formula (II); B) formula (III); C) formula (IV); and D) formula (V); wherein Y, Ar1, Ar2, AP, R4, R5, R6, R7, R6, R9, R9a, R10, R", R12, R17, ring A, and p are as defined in the specification; pharmaceutical compositions containing effective amounts of said compounds or their salts are useful for treating PPAR, specifically PPAR α/γ related disorders, such as diabetes, dyslipidemia, obesity and inflammatory disorders.

WO 2004/092145 A1

(74) Agents: WOOD, David, J. et al.; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

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

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

Published:
— *with international search report*

(88) Date of publication of the revised international search report: 12 May 2005

(15) Information about Correction:
see PCT Gazette No. 19/2005 of 12 May 2005, Section II

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.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2004/001159

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D263/32 C07C59/125 C07D401/04 C07D411/12 C07D249/06
C07D213/66 C07C61/04 C07D307/79 C07D413/14 C07D417/14
C07D405/06 C07D413/12

According to International Patent Classification (IPC) or to both national classification and IPC

CORRECTED VERSION

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/064130 A (PFIZER PROD INC ; HAYWARD CHERYL MYERS (US); PERRY DAVID AUSTEN (US)) 22 August 2002 (2002-08-22) page 2, line 19 - line 21 page 2, formula I page 16, line 18 - line 22 -----	1,3,8,9, 14,15
A	EP 1 088 824 A (PFIZER PROD INC) 4 April 2001 (2001-04-04) page 3, line 56 - line 58 page 4, Formula I page 18, line 14 page 18, line 18 - line 20 -----	1-15

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 March 2005	08. 03. 2005
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Hoepfner, W

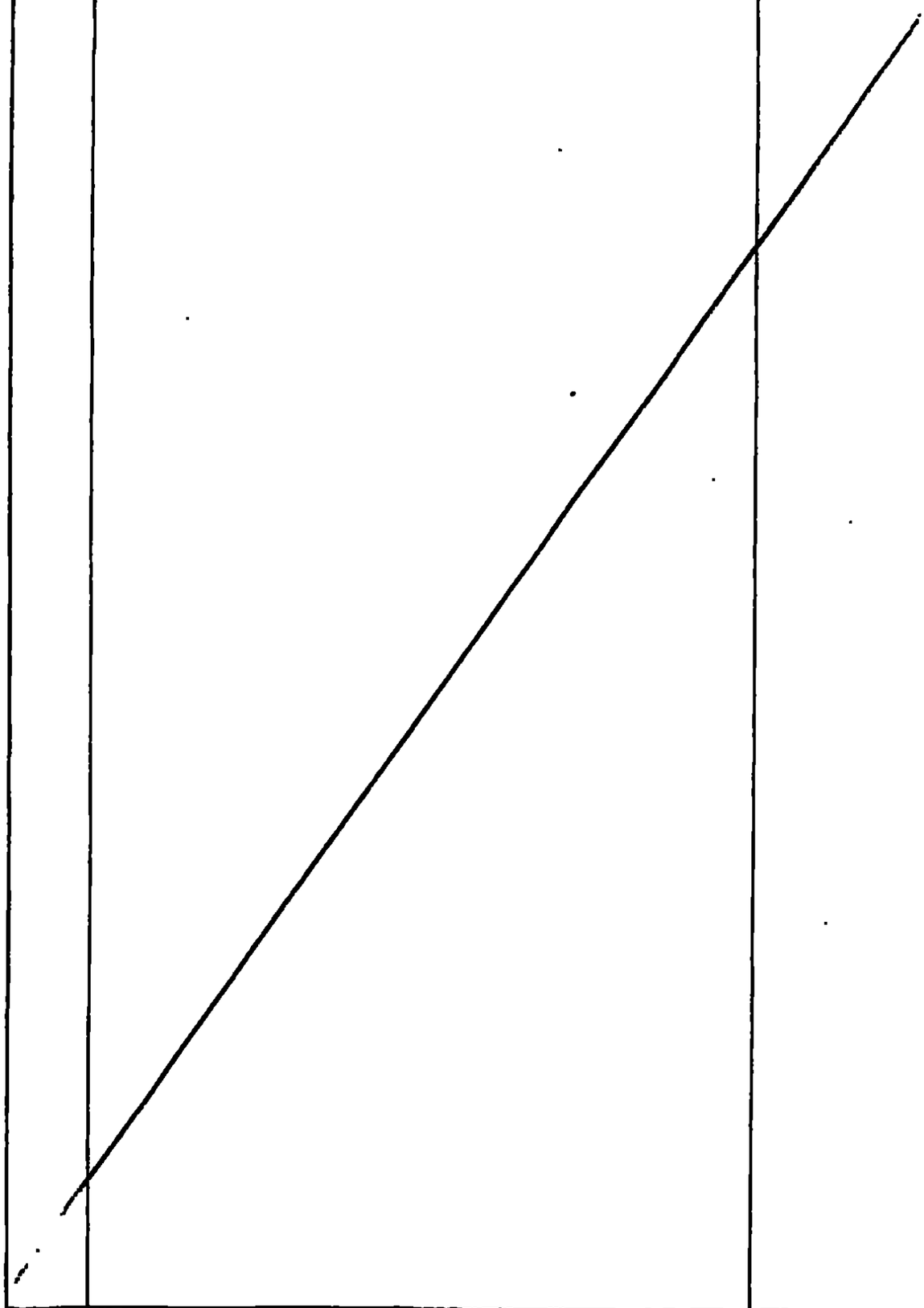
Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2004/001159

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.



2

10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2004/001159

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

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

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

Although claim 14 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2004/001159

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 02064130 A	22-08-2002	BR 0207227 A	10-02-2004
		CA 2438492 A1	22-08-2002
		EP 1372632 A1	02-01-2004
		WO 02064130 A1	22-08-2002
		JP 2004520397 T	08-07-2004
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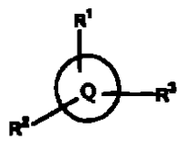
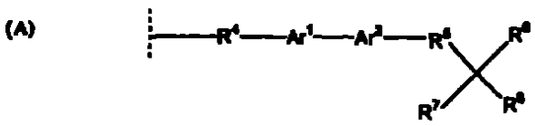
[Continued on next page]

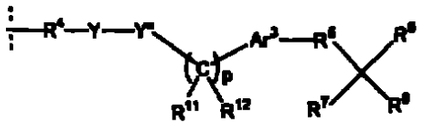
(54) Title: ALPHA SUBSTITUTED CARBOXYLIC ACID AS PPAR MODULATORS



(I)



(A)



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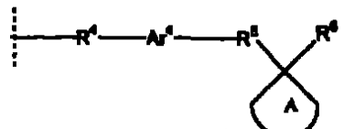

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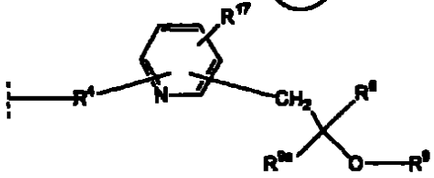

(D)

(57) Abstract: Alpha substituted carboxylic acids of formula (I): wherein R1 and R2 are as defined in the specification and R3 is A) formula (II); B) formula (III); C) formula (IV); and D) formula (V); wherein Y, Ar1, Ar2, AP, R4, R5, R6, R7, R8, R9, R9a, R10, R11, R12, R17, ring A, and p are as defined in the specification; pharmaceutical compositions containing effective amounts of said compounds or their salts are useful for treating PPAR, specifically PPAR α/γ related disorders, such as diabetes, dyslipidemia, obesity and inflammatory disorders.

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ALPHA SUBSTITUTED CARBOXYLIC ACIDS AS PPAR MODULATORS

Background of The Invention

This invention relates to alpha substituted carboxylic acids that modulate the activities of peroxisome proliferator-activated receptor (PPAR), preferably two or more of PPAR-α, PPAR-δ, or PPAR-γ, enabling them to be useful in modulation of blood glucose and the increase of insulin sensitivity in mammals. This invention also relates to treatment of PPAR related disorders, such as diabetes, dyslipidemia, obesity and inflammatory disorders.

Peroxisome proliferators are a structurally diverse group of compounds which, when administered to rodents, elicit dramatic increases in the size and number of hepatic and renal peroxisomes, as well as concomitant increases in the capacity of peroxisomes to metabolize fatty acids via increased expression of the enzymes required for the β-oxidation cycle. Chemicals included in this group are the fibrate class of hypolipidemic drugs, herbicides, and phthalate plasticizers (Reddy and Lalwani, *Crit. Rev. Toxicol.*, 12:1-58 (1983)). Peroxisome proliferation can also be elicited by dietary or physiological factors such as a high-fat diet and cold acclimatization.

Insight into the mechanism whereby peroxisome proliferators exert their pleiotropic effects was provided by the identification of a member of the nuclear hormone receptor superfamily activated by these chemicals (Isseman and Green, *Nature*, 347-645-650 (1990)). This receptor, termed PPAR-α, was subsequently shown to be activated by a variety of medium and long-chain fatty acids and to stimulate expression of the genes encoding rat acyl-CoA oxidase and hydratase-dehydrogenase (enzymes required for peroxisomal β-oxidation), as well as rabbit cytochrome P450 4A6, a fatty acid Ω-hydroxylase.

PPAR-α activates transcription by binding to DNA sequence elements, termed peroxisome proliferator response elements (PPRE), as a heterodimer with the retinoid X receptor. The retinoid X receptor is activated by 9-cis retinoic acid (see Kliewer, et al., *Nature*, 358:771-774 (1992), Gearing, et al., *Proc. Natl. Acad. Sci. USA*, 90:1440-1444 (1993), Keller, et al., *Proc. Natl. Acad. Sci. USA*, 90:2160-2164 (1993), Heyman, et al., *Cell*, 68:397-406 (1992), and Levin, et al., *Nature*, 355:359-361 (1992)). Since the PPAR-α-RXR complex can be activated by peroxisome proliferators and/or 9-cis retinoic acid, the retinoid and fatty acid signaling pathways are seen to converge in modulating lipid metabolism.

Since the discovery of PPAR-α, additional isoforms of PPAR have been identified, e.g., PPAR-δ, or PPAR-γ, which are spatially differentially expressed. Each PPAR receptor shows a different pattern of tissue expression, and

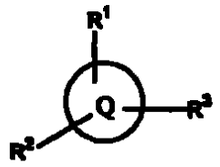
differences in activation by structurally diverse compounds. PPAR-γ, for instance, is expressed most abundantly in adipose tissue and at lower levels in skeletal muscle, heart, liver, intestine, kidney, vascular endothelial and smooth muscle cells as well as macrophages. Two isoforms of PPAR-γ exist, identified as γ_1 and γ_2, respectively. PPAR-γ mediates adipocyte signaling, lipid storage, and fat metabolism. Evidence gathered to date support the conclusion that PPAR-γ is the primary, and perhaps the only, molecular target mediating the insulin sensitizing action of one class of antidiabetic agents, the thiazolidine 2,4 diones.

In a monotherapeutic or combination therapy context, new and established oral antidiabetic agents are still considered to have non-uniform and even limited effectiveness. The effectiveness of oral antidiabetic therapies may be limited, in part, because of poor or limited glycemic control, or poor patient compliance due to unacceptable side effects. These side effects include edema, weight gain, or even more serious complications. For instance, hypoglycemia is observed in some patients taking sulfonylureas. Metformin, a substituted biguanide, can cause diarrhea and gastrointestinal discomfort. Finally, edema, weight gain, and in some cases, hepatotoxicity, have been linked to the administration of some thiazolidine 2,4 dione antidiabetic agents. Combination therapy using two or more of the above agents is common, but generally only leads to incremental improvements in glycemic control.

As a result, there is a need for antidiabetic agents that display combined PPAR-α and PPAR-γ activation which should lead to the discovery of efficacious glucose and triglyceride lowering drugs that have great potential in the treatment of type 2 diabetes and the metabolic syndrome (i.e., impaired glucose tolerance, insulin resistancem hyoertriglyceridemia and/or obesity).

Summary of The Invention

The present invention provides novel compounds of Formula (I):



(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

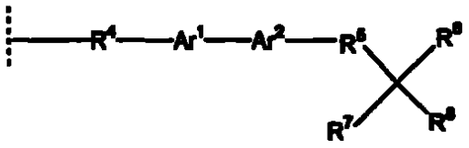
Ring Q is $(C_6$-$C_{10})$aryl or (4-10)-membered heterocyclyl;

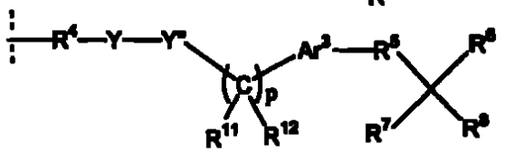
R^1 is H, halo, $(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$alkoxy, CN, CF_3, -O-CF_3, -O-SO_2-$(C_1$-$C_8)$alkyl, -O-SO_2-$(CR^{11}R^{12})_t(C_6$-$C_{10})$aryl, -$(CR^{11}R^{12})_t(C_3$-$C_{10})$cycloalkyl-$(CR^{11}R^{12})_t$, -$(CR^{11}R^{12})_t(C_3$-$C_{10})$cycloalkyl-$(CR^{11}R^{12})_t$-O-, -$(CR^{11}R^{12})_t(C_6$-$C_{10})$aryl-$(CR^{11}R^{12})_t$, -$(CR^{11}R^{12})_t(C_6$-$C_{10})$aryl-$(CR^{11}R^{12})_t$-O-,

-$(CR^{11}R^{12})_r$-(4-10)-membered heterocyclyl-$(CR^{11}R^{12})_t$, or -$(CR^{11}R^{12})_r$-(4-10)-membered heterocyclyl-$(CR^{11}R^{12})_t$-O-; wherein the ring carbon atoms of R^1 are optionally substituted by 1 to 3 R^{13} groups; and the ring nitrogen atoms of R^1 are optionally substituted by 1 to 3 (C_1-C_6)alkyl;

R^2 is H, (C_1-C_6)alkyl, -$(CR^{11}R^{12})_r$-(C_3-C_{10})cycloalkyl, -$(CR^{11}R^{12})_r$-(C_6-C_{10})aryl, or -$(CR^{11}R^{12})_t$(4-10)-membered heterocyclyl; and wherein the carbon atoms of R^2 are optionally substituted by 1 to 3 R^{13} groups; and the ring nitrogen atoms of R^2 are optionally substituted by 1 to 3 (C_1-C_6)alkyl;

R^3 is selected from the group consisting of:

A)  ;

B)  ;

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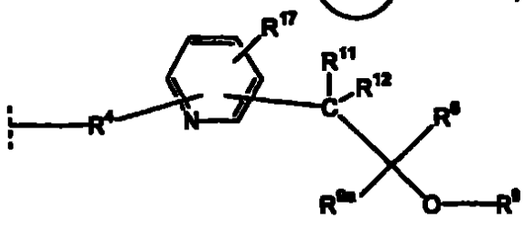
D)  ;

Y is -(C=O)- or -SO_2-;

Y" is NR^{10} or –O-;

p is 0, 1, or 2;

each q, r, and t are independently 0, 1, 2, 3, 4, or 5;

each n is independently 0, 1, 2, 3, or 4;

each k is independently 1, 2, or 3;

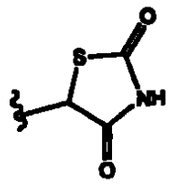
each m and s are independently 0, 1, 2, or 3;

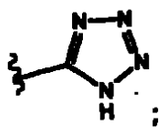
each j is 0, 1, or 2;

Each R^4 is –$(CR^{11}R^{12})_m$-, -$(CR^{11}R^{12})_m$-S-$(CR^{11}R^{12})_n$-, –$(CR^{11}R^{12})_m$-NR^{10}-, -$(CR^{11}R^{12})_m$-NR^{10}-$(CR^{11}R^{12})_n$-O-, -$(CR^{11}R^{12})_n$-O-$(CR^{11}R^{12})_k$-NR^{10}-, -$(CR^{11}R^{12})_n$-O-$(CR^{11}R^{12})_m$-, -$(CR^{11}R^{12})_n$-O-$(CR^{11}R^{12})_k$-O-$(CR^{11}R^{12})_m$-, -$(CR^{11}R^{12})_n$-CR^{11}=CR^{12}-$(CR^{11}R^{12})_m$-, or -CH=CH-$(CR^{11}R^{12})$-O-$(CH_2)_m$-;

Each R^6 is a bond or $-(CR^{11}R^{12})_m-Z-(CR^{11}R^{12})_n$; wherein Z is $-CR^{11}R^{12}-$, -O-, $-NR^{10a}-$, or $-S(O)_j-$;

Each R^8 is -(C=O)-OH, $-(C=O)-OM^+$, $-(C=O)-(C_1-C_8)$alkyl, $-(C=O)-O-(C_1-C_8)$alkyl, $-(C=O)-NR^{10}R^{11}$, $-(C=O)-NR^{10}-SO_2-R^{11}$, $-SO_2-NH-R^{10}$, $-NH-SO_2-R^{10}$, -(C=O)-NH-C=N, or R^8 has a formula:



; or


;

M^+ is an alkali metal cation or an alkaline earth metal cation;

Each R^7 and R^8 is independently H, (C_1-C_8)alkyl, (C_1-C_8)alkoxy, $-(CR^{11}R^{12})_t(C_3-C_{10})$cycloalkyl, $-(CR^{11}R^{12})_t(C_6-C_{10})$aryl, $-(CR^{11}R^{12})_t(C_6-C_{10})$aryl-O-, $-(CR^{11}R^{12})_t$(4-10)-membered heterocyclyl or $-(CR^{11}R^{12})_t$(4-10)-membered heterocyclyl-O-;

Or R^7 and R^8 may optionally be taken together with the carbon to which they are attached to form a (C_3-C_{10})cycloalkyl or a (3-10)-membered heterocyclyl;

Each of Ar^1, Ar^2, Ar^3, and Ar^4 represents (C_6-C_{10})aryl or (5-10)-membered heterocyclyl; wherein the ring carbon atoms of each of Ar^1, Ar^2, Ar^3, and Ar^4 are optionally substituted by 1 to 3 R^{13} groups;

Ring A represents a 3, 4, 5, 6 or 7-membered ring optionally containing 1 to 4 heteroatoms which may be the same or different and which are selected from $-N(R^{10a})-$, O, and $S(O)_j$, wherein j is 0, 1, or 2, with the proviso that the ring does not contain two adjacent O or $S(O)_j$ atoms, and wherein the carbon atoms of the ring A moiety are optionally substituted by 1 to 3 R^{13} groups;

R^9 is (C_1-C_8)alkyl, $-(CR^{11}R^{12})_t(C_6-C_{10})$aryl or $-(CR^{11}R^{12})_t$(4-10)-membered heterocyclyl, wherein t is independently 0, 1, 2, 3, 4, or 5, wherein said R^9 groups are substituted with 1 to 3 groups independently selected from $-(CR^{11}R^{12})_sNR^{10}R^{11}$, $-(CR^{11}R^{12})_sNR^{10}(C_1-C_8)$alkanoyl, $-(CR^{11}R^{12})_sO(CR^{11}R^{12})_tR^{10}$, and $-(CR^{11}R^{12})_sR^{10}$; and wherein the heterocyclyl, aryl and alkyl moieties of the foregoing groups are optionally substituted with 1 to 3 R^{13} groups;

R^{8a} and R^{10} are independently H or (C_1-C_8)alkyl;

R^{11} and R^{12} are independently H, (C_1-C_8)alkyl, hydroxy, or (C_1-C_8)alkoxy;

R^{10a} is selected from H, (C_1-C_8)alkyl, $-(C=O)-R^{14}$, $-SO_2NR^{15}R^{16}$, or $-S(O)_j(C_1-C_8)$alkyl;

Each R^{13} and R^{13a} are independently selected from the group consisting of halo, cyano, nitro, trifluoromethoxy, trifluoromethyl, azido, hydroxy, (C_1-C_8)alkoxy, (C_1-C_{10})alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, $-O-(CR^{11}R^{12})_s-O-(CR^{11}R^{12})_{s'}-$, -(C=O)-

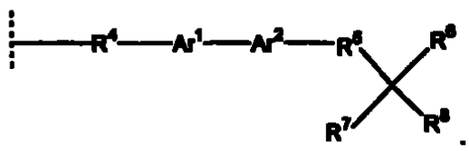
R^{14}, -(C=O)-O-R^{15}, -O-(C=O)-R^{15}, -NR^{15}(C=O)-R^{16}, -NR^{15}(C=O)-O-R^{16}, -(C=O)-$NR^{15}R^{16}$, -$NR^{15}R^{16}$, -$NR^{15}OR^{16}$, -$SO_2NR^{15}R^{16}$, -S(O)$_t$(C_1-C_8)alkyl, -O-SO_2-R^{14}, -NR^{15}-SO_2-R^{16}, R^{15}-$(CR^{11}R^{12})_t$(C_6-C_{10} aryl), -$(CR^{11}R^{12})_t$(4-10)-membered heterocyclyl, -$(CR^{11}R^{12})_q$(C=O)$(CR^{11}R^{12})_t$(C_6-C_{10})aryl, -$(CR^{11}R^{12})_q$(C=O)$(CR^{11}R^{12})_t$(4-10)-membered heterocyclyl, -$(CR^{11}R^{12})_q$O$(CR^{11}R^{12})_t$(C_6-C_{10})aryl, -$(CR^{11}R^{12})_q$O$(CR^{11}R^{12})_q$(4-10)-membered heterocyclyl, -$(CR^{11}R^{12})_q$$SO_2$$(CR^{11}R^{12})_t$($C_6$-$C_{10}$)aryl, and -$(CR^{11}R^{12})_q$$SO_2$$(CR^{11}R^{12})_t$(4-10)-membered heterocyclyl; 1 or 2 ring carbon atoms of the heterocyclic moieties of the foregoing R^{13} and R^{13a} groups are optionally substituted with an oxo (=O) moiety, and the alkyl, alkenyl, alkynyl, aryl and heterocyclic moieties of the foregoing R^{13} and R^{13a} groups are optionally substituted with 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, -OR^{15}, -(C=O)-R^{15}, -(C=O)-O-R^{15}, -O-(C=O)-R^{15}, -NR^{15}(C=O)-R^{16}, -(C=O)-$NR^{15}R^{16}$, -$NR^{15}R^{16}$, -$NR^{15}OR^{16}$, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, -$(CR^{11}R^{12})_t$(C_6-C_{10})aryl, and -$(CR^{11}R^{12})_t$(4-10)-membered heterocyclyl;

each R^{14}, R^{15}, and R^{16} is independently selected from H, (C_1-C_8)alkyl, -$(CR^{11}R^{12})_t$(C_6-C_{10})aryl, and -$(CR^{11}R^{12})_t$(4-10)-membered heterocyclyl; 1 or 2 ring carbon atoms of the heterocyclic group are optionally substituted with an oxo (=O) moiety, and the alkyl, aryl and heterocyclic moieties of the foregoing R^{14}, R^{15} and R^{16} groups are optionally substituted with 1 to 3 substituents independently selected from halo, cyano, nitro, -$NR^{11}R^{12}$, trifluoromethyl, trifluoromethoxy, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, hydroxy, and (C_1-C_8) alkoxy;

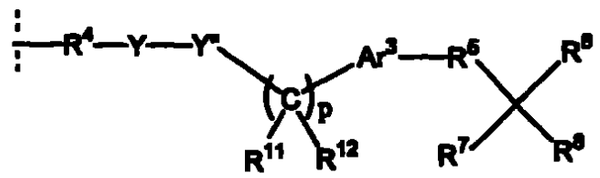
R^{17} is H, (C_1-C_8)alkyl, -O-(C_1-C_8)alkyl, halo, CN, OH, CF_3, or –O-CF_3;

and wherein any of the above-mentioned substituents comprising a CH_3 (methyl), CH_2 (methylene), or CH (methine) group which is not attached to a halo, SO or SO_2 group or to a N, O or S atom optionally bears on said group a substituent selected from hydroxy, halo, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, –NH_2, -NH(C_1-C_8)alkyl, and -N((C_1-C_8)alkyl)$_2$.

In one embodiment, the invention relates to compounds of the Formula I wherein R^3 is

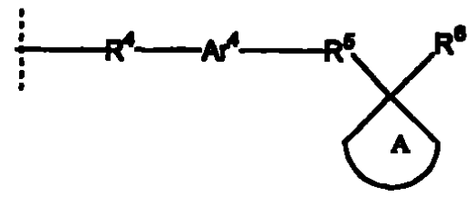
A) 

In another embodiment, the invention relates to compounds of the Formula I wherein R^3 is

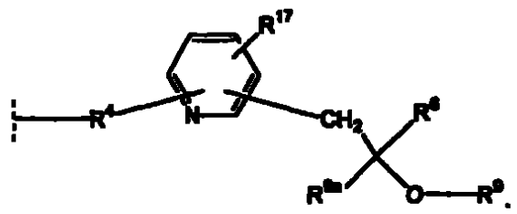
B) 

Within this embodiment, preferred $-R^4-Y-Y''-$ are $-(CR^{11}R^{12})_n-O-(CR^{11}R^{12})_m-(C=O)-NR^{10}-$ or $-(CR^{11}R^{12})_m-NR^{10}-(C=O)-O-$.

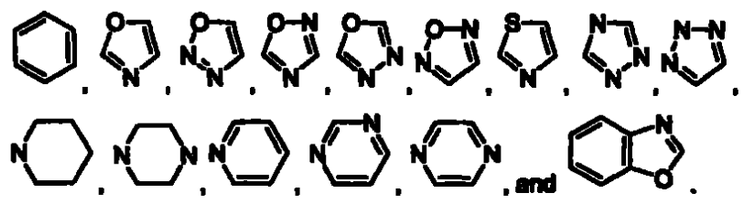
In another embodiment, the invention relates to compounds of the Formula I wherein R^3 is

C) 

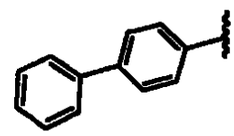
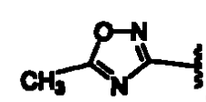
In another embodiment, the invention relates to compounds of the Formula I wherein R^3 is

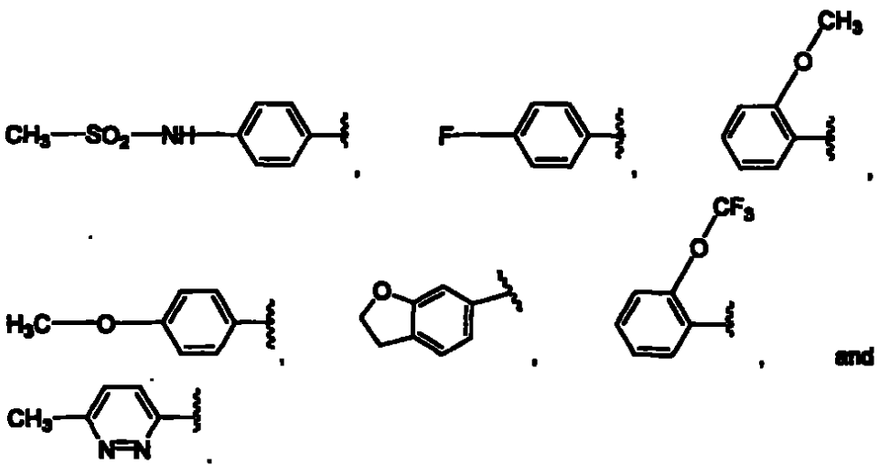
D) 

In another embodiment, the invention relates to compounds of the Formula I wherein ring Q is selected from the group consisting of



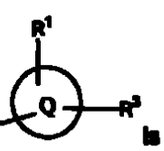
In another embodiment, the invention relates to compounds of the Formula I wherein R^1 is H, halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, CF_3, $-O-CF_3$, $-O-SO_2-(C_1-C_6)$alkyl, $-O-SO_2-(CR^{11}R^{12})_n(C_6-C_{10})$aryl, or $-(CR^{11}R^{12})_n(C_6-C_{10})$aryl-O-, wherein the ring carbon atoms of R^1 are optionally substituted by 1 to 3 R^{13} groups.

In another embodiment, the invention relates to compounds of the Formula I wherein R^2 is H, phenyl,  ,  .

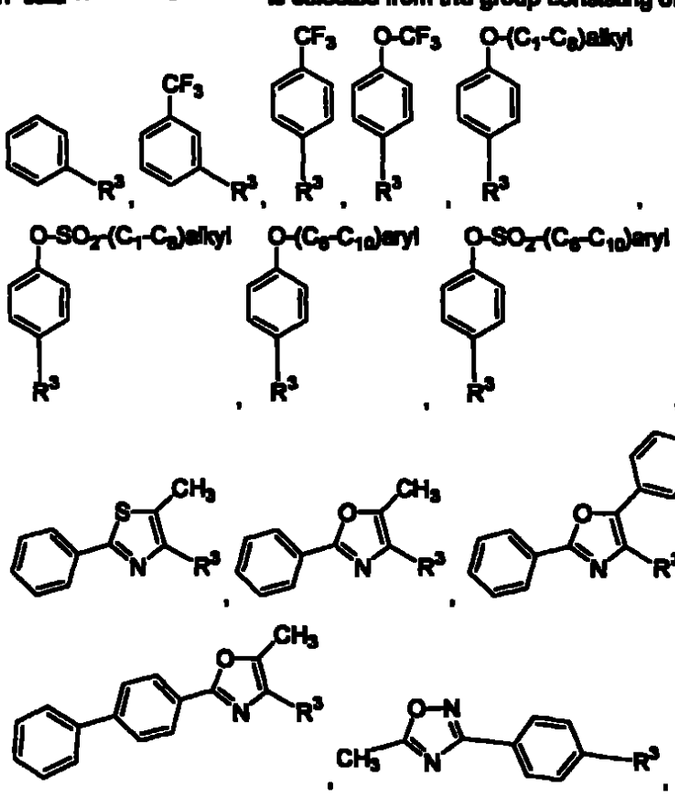


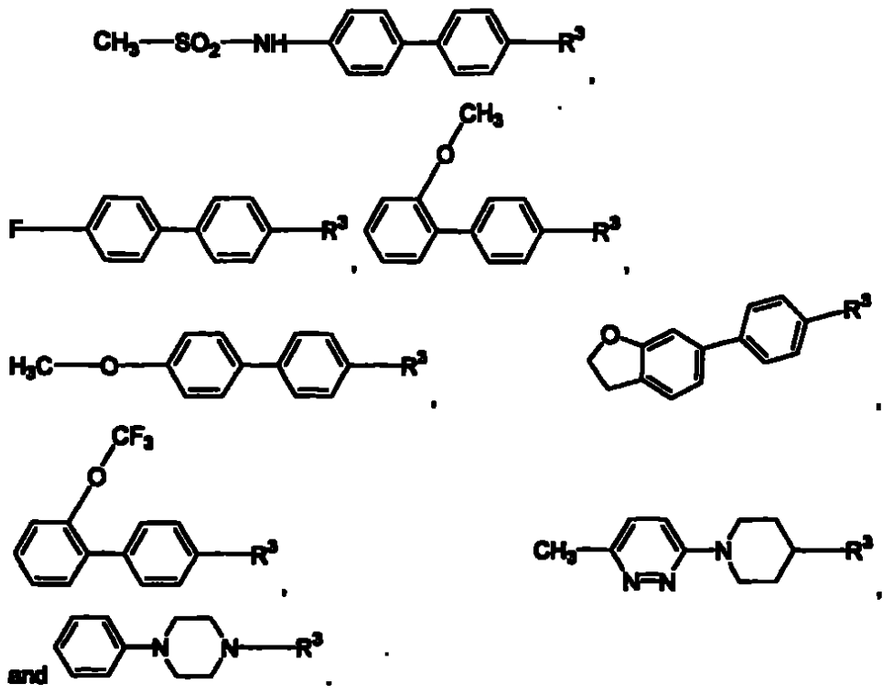
and

In another embodiment, the invention relates to compounds of the Formula



I wherein said R^2 is selected from the group consisting of:





and

In another embodiment, the invention relates to compounds of the Formula I wherein R^4 is $-CH_2-O-$, $-CH_2-O-CH_2-$, $-CH_2-CH_2-O-$, $-CH=CH-CH_2-O-$, or $-CH_2-CH_2-CH_2-O-$.

In another embodiment, the invention relates to compounds of the Formula I wherein R^4 is $-(CH_2)_n-$; wherein n is independently 0, 1, 2, or 3.

In another embodiment, the invention relates to compounds of the Formula I wherein R^5 is a bond or $-(CR^{11}R^{12})_m-Z-(CR^{11}R^{12})_s-$; wherein Z is -O-, $-NR^{10a}-$, or $-S(O)_j-$; wherein each m and s are independently 0, 1, 2, or 3; and wherein j is 0, 1, or 2.

In another embodiment, the invention relates to compounds of the Formula I wherein R^5 is a bond, -O-, $-CH_2-$, $-C(CH_3)H-$, $-C(OH)H-$, or $-C(O-(C_1-C_8)alkyl)H-$.

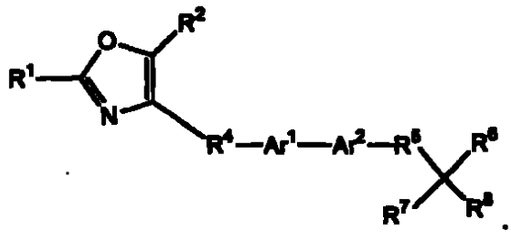
In another embodiment, the invention relates to compounds of the Formula I wherein R^6 is $-(C=O)-OH$.

In another embodiment, the invention relates to compounds of the Formula I wherein R^6 is $-(C=O)-OM^+$, wherein M^+ is selected from the group consisting of Ca^{++}, Li^+, Na^+ and K^+.

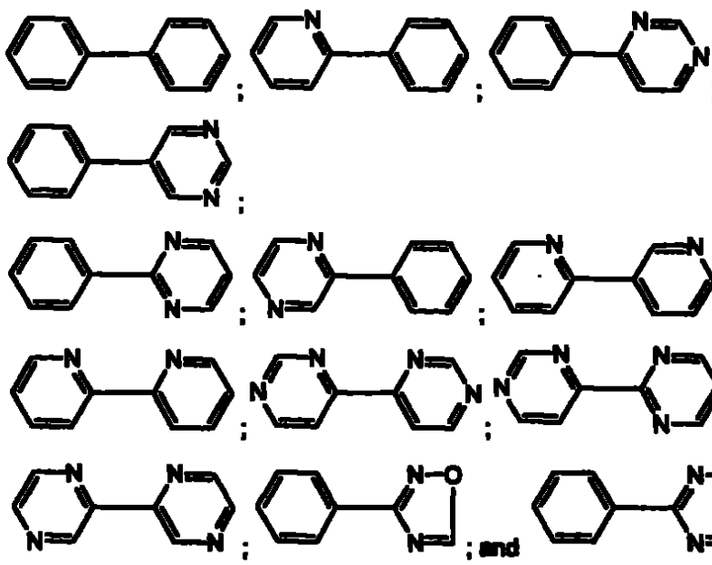
In another embodiment, the invention relates to compounds of the Formula I wherein each R^7 and R^8 is independently H, $(C_1-C_8)alkyl$, or $(C_1-C_8)alkoxy$.

In another embodiment, the invention relates to compounds of the Formula I wherein each R^7 and R^8 are taken together with the carbon to which they are attached to form a (3-7)-membered heterocyclyl.

In another embodiment, the invention relates to compounds having a formula:

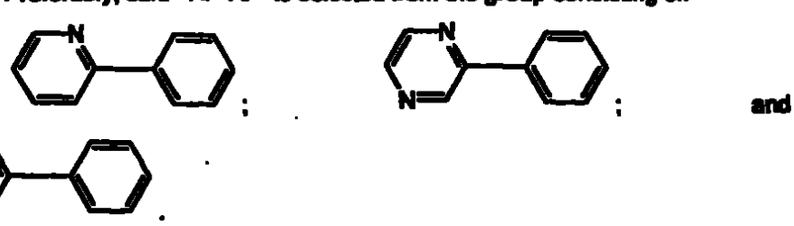


Within this embodiment, the invention relates to compounds wherein said $-Ar^1-Ar^2-$ is selected from the group consisting of:



wherein the ring carbon atoms of each of Ar^1 and Ar^2 are optionally substituted by 1 to 3 R^{13} groups selected from the group consisting of halo, (C_1-C_6)alkyl, and (C_1-C_6)alkoxy.

Preferably, said $-Ar^1-Ar^2-$ is selected from the group consisting of:



Within this embodiment, specific compounds of the present invention are selected from the group consisting of

2-Methyl-2-({3'-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-1,1'-biphenyl-3-yl}oxy)propanoic acid;

2-Methyl-2-[(3'-{[4-(trifluoromethyl)benzyl]oxy}-1,1'-biphenyl-3-yl)oxy]propanoic acid;

2-Methyl-2-[(3'-[2-[1-(6-methylpyridazin-3-yl)piperidin-4-yl]ethoxy}-1,1'-biphenyl-3-yl)oxy]propanoic acid;

1-({3'-[2-(5-Methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-1,1'-biphenyl-3-yl}oxy)cyclobutanecarboxylic acid;

2-({3'-[2-(5-Methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-1,1'-biphenyl-3-yl}oxy)butanoic acid;

2-(3-{6-[2-(5-Methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridin-2-yl}phenoxy)butanoic acid;

1-(3-{6-[2-(5-Methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridin-2-yl}phenoxy)cyclobutanecarboxylic acid;

2-Methyl-2-(3-{6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridin-2-yl}phenoxy)propanoic acid;

2-Methyl-2-(3-{6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyrazin-2-yl}phenoxy)propanoic acid; and

and pharmaceutically acceptable salts thereof.

Within this embodiment, a specific compound of the present invention is 1-({3'-[2-(5-Methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-1,1'-biphenyl-3-yl}oxy)cyclobutanecarboxylic acid or the pharmaceutically acceptable salts thereof.

Within this embodiment, a specific compound of the present invention is 2-({3'-[2-(5-Methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-1,1'-biphenyl-3-yl}oxy)butanoic acid or the pharmaceutically acceptable salts thereof.

Within this embodiment, a specific compound of the present invention is 2-(3-{6-[2-(5-Methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridin-2-yl}phenoxy)butanoic acid or the pharmaceutically acceptable salts thereof.

Within this embodiment, a specific compound of the present invention is 1-(3-{6-[2-(5-Methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridin-2-yl}phenoxy)cyclobutanecarboxylic acid or the pharmaceutically acceptable salts thereof.

Within this embodiment, a specific compound of the present invention is 1-[(3'-{[2-(3-fluorophenyl)-5-methyl-1, 3-oxazol-4-yl]methoxy}biphenyl-3-yl)oxy]cyclobutanecarboxylic acid or the pharmaceutically acceptable salts thereof.

Within this embodiment, a specific compound of the present invention is 1-({3'-[3-(5-methyl-2-phenyl-1, 3-oxazol-4-yl)propoxy]biphenyl-3-yl}oxy)cyclobutanecarboxylic acid or the pharmaceutically acceptable salts thereof.

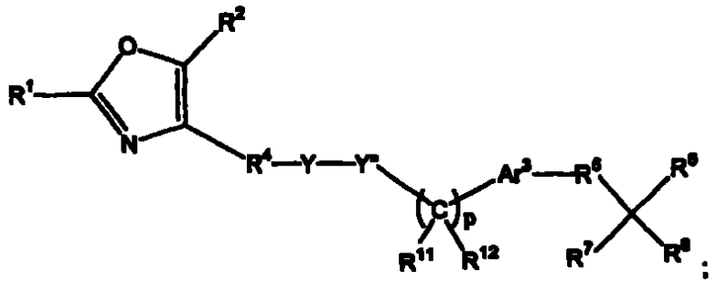
Within this embodiment, a specific compound of the present invention is 1-[(3'-{[5-(4-methoxyphenyl)-1,2,4-oxadiazol-3-yl]methoxy}biphenyl-3-yl)oxy]cyclobutanecarboxylic acid or the pharmaceutically acceptable salts thereof.

Within this embodiment, a specific compound of the present invention is 2-[(3'-{2-[2-(3-Fluorophenyl)-5-methyl-1,3-oxazol-4-yl]ethoxy}biphenyl-3-yl)oxy]-2-methylpropanoic acid or the pharmaceutically acceptable salts thereof.

Within this embodiment, a specific compound of the present invention is 2-methyl-2-({3'-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]biphenyl-3-yl}oxy)propanoic acid or the pharmaceutically acceptable salts thereof.

Within this embodiment, a specific compound of the present invention is 2-ethoxy-3-{3'-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]biphenyl-3-yl}propanoic acid or the pharmaceutically acceptable salts thereof.

In another embodiment, the invention relates to compounds having a formula:



wherein Y is -(C=O)- or $-SO_2-$, Y'' is NR^{10}, and p is 1.

Preferably, each of R^{11} and R^{12} are independently H.

Preferably, Ar^3 is phenyl.

Within this embodiment, specific compounds of the present invention are selected from the group consisting of

1-(3-{[({2-[3-(Trifluoromethyl)phenyl]ethoxy}carbonyl)amino]methyl}phenoxy) cyclobutanecarboxylic acid;

2-(3-{[({2-[3-(Trifluoromethyl)phenyl]ethoxy}carbonyl)amino]methyl}phenoxy)butanoic acid;

2-Methyl-2-(3-{[({2-[3-(trifluoromethyl)phenyl]ethoxy}carbonyl)amino]methyl}phenoxy) propanoic acid;

2-Methyl-2-{3-[({[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]carbonyl}amino)methyl] phenoxy}propanoic acid;

2-Methyl-2-(3-[[([4-(5-methyl-1,2,4-oxadiazol-3-yl)benzyl]oxy}carbonyl)amino]methyl} phenoxy)propanoic acid;

2-{3-[({[2-(5-Methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]carbonyl}amino)methyl]phenoxy} butanoic acid;

1-[3-[({[2-(5-Methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]carbonyl}amino)methyl]phenoxy} cyclobutanecarboxylic acid;

1-[3-[({[3-(5-Methyl-2-phenyl-1,3-oxazol-4-yl)propoxy]carbonyl}amino)methyl]phenoxy} cyclobutanecarboxylic acid;

2-[3-[({[3-(5-Methyl-2-phenyl-1,3-oxazol-4-yl)propoxy]carbonyl}amino)methyl] phenoxy}butanoic acid;

2-Methyl-2-[3-[({[3-(5-methyl-2-phenyl-1,3-oxazol-4-yl)propoxy]carbonyl}amino)methyl] phenoxy}propanoic acid;

and pharmaceutically acceptable salts thereof.

Within this embodiment, a specific compound of the present invention is 2-Methyl-2-[3-[({[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]carbonyl}amino)methyl]phenoxy}propanoic acid or the pharmaceutically acceptable salts thereof.

Within this embodiment, a specific compound of the present invention is 2-methyl-2-[3-[({[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]carbonyl}amino)methyl]phenoxy}propanoic acid or the pharmaceutically acceptable salts thereof.

Within this embodiment, a specific compound of the present invention is 2-methyl-2-[4-[({[3-(5-methyl-2-phenyl-1,3-oxazol-4-yl)propoxy]carbonyl}amino)methyl]phenoxy}propanoic acid or the pharmaceutically acceptable salts thereof.

Within this embodiment, a specific compound of the present invention is 2-{3-fluoro-4-[({[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]carbonyl}amino)methyl]phenoxy}-2-methylpropanoic acid or the pharmaceutically acceptable salts thereof.

Within this embodiment, a specific compound of the present invention is 2-{3-[({[2-(5-Methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]carbonyl}amino)methyl]phenoxy}butanoic acid or the pharmaceutically acceptable salts thereof.

Within this embodiment, a specific compound of the present invention is 2-{3-[({[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]carbonyl}amino)methyl]phenoxy}butanoic acid or the pharmaceutically acceptable salts thereof.

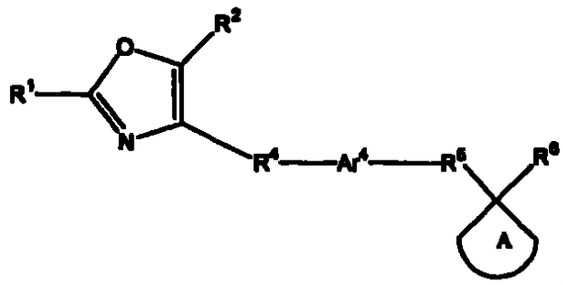
Within this embodiment, a specific compound of the present invention is 1-{3-[({[2-(5-Methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]carbonyl}amino)methyl]phenoxy}cyclobutanecarboxylic acid or the pharmaceutically acceptable salts thereof.

Within this embodiment, a specific compound of the present invention is 2-methyl-2-(3-[({[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethyl]amino}carbonyl)oxy]methyl}phenoxy)propanoic acid or the pharmaceutically acceptable salts thereof.

Within this embodiment, a specific compound of the present invention is 2-ethoxy-3-{3-[({[3-(5-methyl-2-phenyl-1,3-oxazol-4-yl)propoxy]carbonyl}amino)methyl]phenyl}propanoic acid or the pharmaceutically acceptable salts thereof.

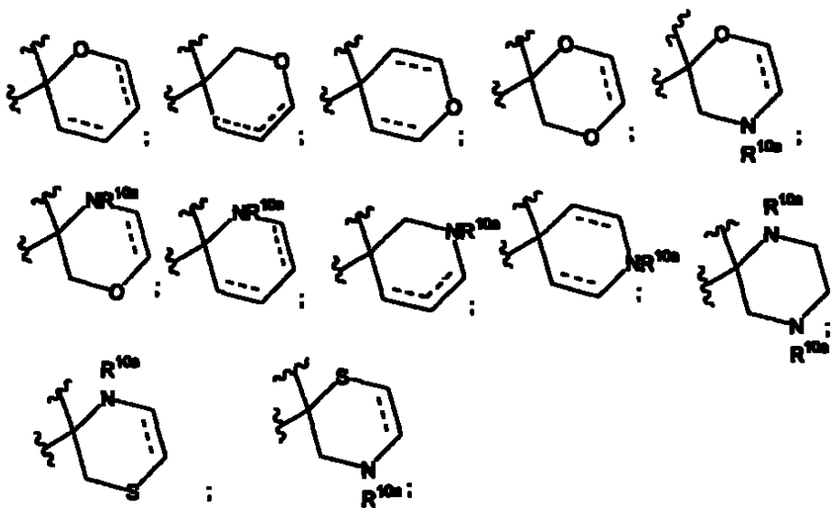
Within this embodiment, a specific compound of the present invention is 2-ethoxy-3-{3-[({[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]carbonyl}amino)methyl]phenyl}propanoic acid or the pharmaceutically acceptable salts thereof.

In another embodiment, the invention relates to compounds having a formula:



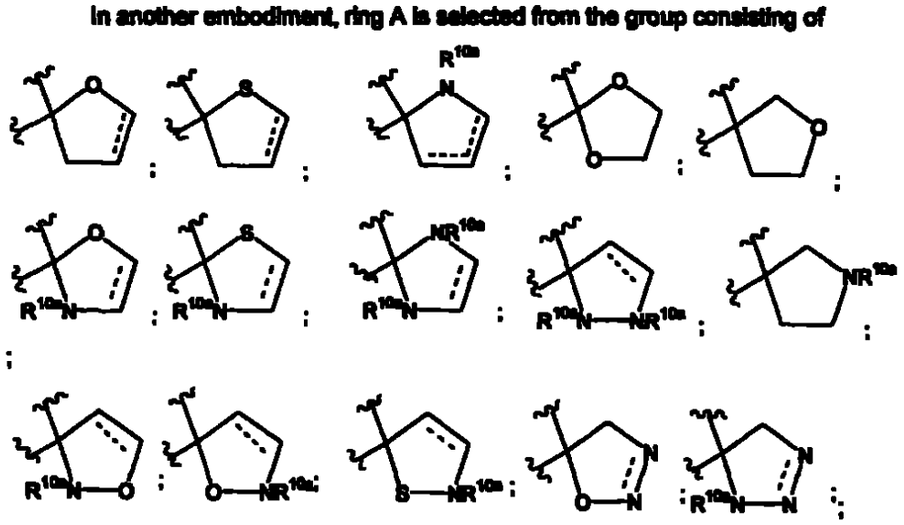
In another embodiment, ring A is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

In another embodiment, ring A is selected from the group consisting of



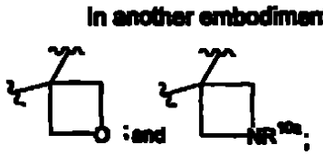
wherein — is an optional double bond.

In another embodiment, ring A is selected from the group consisting of



wherein — is an optional double bond.

In another embodiment, ring A is selected from the group consisting of



wherein — is an optional double bond.

Within this embodiment, Ar^4 is phenyl, naphthyl, pyridinyl, pyrimidinyl, or pyrazinyl.

Within this embodiment, specific compounds of the present invention are selected from the group consisting of

1-{4-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]benzyl}cyclohexanecarboxylic acid;

1-{4-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]benzyl}cyclopentanecarboxylic acid;

1-{4-[3-(5-methyl-2-phenyl-1,3-oxazol-4-yl)propoxy]benzyl}cyclopentanecarboxylic acid;

4-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyl}tetrahydro-2H-pyran-4-carboxylic acid;

4-{4-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]benzyl}tetrahydro-2H-pyran-4-carboxylic acid;

1-{4-[2-(4'-methoxy-1,1'-biphenyl-4-yl)ethoxy]benzyl}cyclobutanecarboxylic acid;

1-{4-[2-(4'-fluoro-1,1'-biphenyl-4-yl)ethoxy]benzyl}cyclobutanecarboxylic acid;

1-{4-[2-(2'-methoxy-1,1'-biphenyl-4-yl)ethoxy]benzyl}cyclobutanecarboxylic acid;

1-(4-{2-[3'-(trifluoromethoxy)-1,1'-biphenyl-4-yl]ethoxy}benzyl)cyclobutanecarboxylic acid;

1-(4-{2-[4-(6-methoxypyridin-3-yl)phenyl]ethoxy}benzyl)cyclobutanecarboxylic acid;

1-(4-{2-[4'-(methylsulfonyl)-1,1'-biphenyl-4-yl]ethoxy}benzyl)cyclobutanecarboxylic acid;

1-(4-{2-[4-(2,3-dihydro-1-benzofuran-6-yl)phenyl]ethoxy}benzyl)cyclobutanecarboxylic acid;

1-[4-(2-{4'-[(methylsulfonyl)amino]-1,1'-biphenyl-4-yl}ethoxy)benzyl]cyclobutanecarboxylic acid;

1-{4-[3-(5-methyl-2-phenyl-1,3-oxazol-4-yl)propoxy]benzyl}cyclobutanecarboxylic acid;

1-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyl}cyclobutanecarboxylic acid;

1-{3-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]benzyl}cyclobutanecarboxylic acid;

1-{4-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]benzyl}cyclobutanecarboxylic acid;

1-{4-[(2,5-diphenyl-1,3-oxazol-4-yl)methoxy]benzyl}cyclobutanecarboxylic acid;

1-{4-[3-(2,5-diphenyl-1,3-oxazol-4-yl)propoxy]benzyl}cyclobutanecarboxylic acid;

1-{4-[(2,5-diphenyl-1,3-oxazol-4-yl)methoxy]phenoxy}cyclobutanecarboxylic acid;

1-{4-[3-(2,5-diphenyl-1,3-oxazol-4-yl)propoxy]phenoxy}cyclobutanecarboxylic acid;

1-(4-[2-[2-(1,1'-biphenyl-4-yl)-5-methyl-1,3-oxazol-4-yl]ethoxy]phenoxy)cyclobutanecarboxylic acid;

1-{4-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]phenoxy}cyclobutanecarboxylic acid;

1-{4-[3-(5-methyl-2-phenyl-1,3-oxazol-4-yl)propoxy]phenoxy}cyclobutanecarboxylic acid;

1-{4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]phenoxy}cyclobutanecarboxylic acid;

1-({6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridin-3-yl}methyl)cyclobutanecarboxylic acid;

1-(hydroxy{6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridin-3-yl}methyl)cyclobutanecarboxylic acid;

1-({6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridin-3-yl}methyl)cyclopentanecarboxylic acid;

1-({6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridin-3-yl}methyl)cyclohexanecarboxylic acid;

2-({6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridin-3-yl}methyl)tetrahydrofuran-2-carboxylic acid;

2-({5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridin-2-yl}methyl)tetrahydrofuran-2-carboxylic acid;

and the pharmaceutically acceptable salts thereof.

Within this embodiment, a specific compound of the present invention is 1-{4-[3-(5-methyl-2-phenyl-1,3-oxazol-4-yl)propoxy]benzyl}cyclobutanecarboxylic acid or the pharmaceutically acceptable salts thereof.

Within this embodiment, a specific compound of the present invention is 1-{4-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]benzyl}cyclobutanecarboxylic acid or the pharmaceutically acceptable salts thereof.

Within this embodiment, a specific compound of the present invention is 2-({6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridin-3-yl}methyl)tetrahydrofuran-2-carboxylic acid or the pharmaceutically acceptable salts thereof.

Within this embodiment, a specific compound of the present invention is 2-({5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridin-2-

yl]methyl}tetrahydrofuran-2-carboxylic acid or the pharmaceutically acceptable salts thereof.

Within this embodiment, a specific compound of the present invention is 2-((6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridin-3-yl}methyl)tetrahydro-2*H*-pyran-2-carboxylic acid or the pharmaceutically acceptable salts thereof.

Within this embodiment, a specific compound of the present invention is 2-[(6-{2-[2-(3-chlorophenyl)-5-methyl-1,3-oxazol-4-yl]ethoxy}pyridin-3-yl)methyl]tetrahydrofuran-2-carboxylic acid or the pharmaceutically acceptable salts thereof.

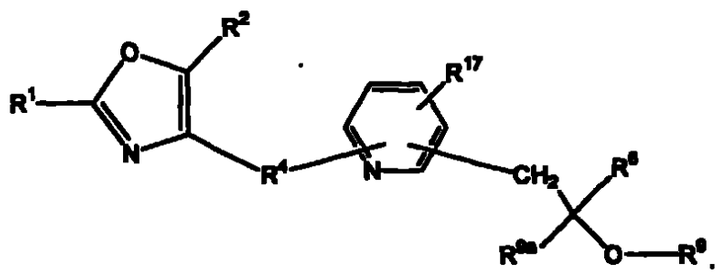
Within this embodiment, a specific compound of the present invention is 2-[(6-{2-[2-(3-methoxyphenyl)-5-methyl-1,3-oxazol-4-yl]ethoxy}pyridin-3-yl)methyl]tetrahydrofuran-2-carboxylic acid or the pharmaceutically acceptable salts thereof.

Within this embodiment, a specific compound of the present invention is 2-{5-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyrazin-2-ylmethyl}-tetrahydro-furan-2-carboxylic acid or the pharmaceutically acceptable salts thereof.

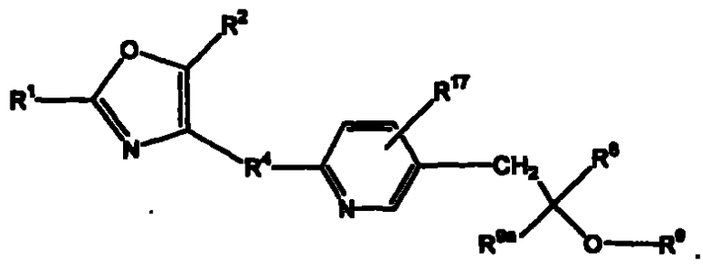
Within this embodiment, a specific compound of the present invention is -{4-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]benzyl}tetrahydrofuran-2-carboxylic acid or the pharmaceutically acceptable salts thereof.

Within this embodiment, a specific compound of the present invention is 2-{6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-naphthalen-2-ylmethyl}-tetrahydro-furan-2-carboxylic acid or the pharmaceutically acceptable salts thereof.

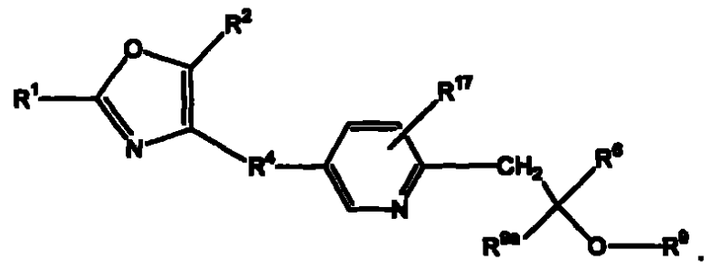
In another embodiment, the invention relates to compounds having a formula:



Within this embodiment, preferably the invention relates to compounds having a formula:



Within this embodiment, preferably the invention relates to compounds having a formula:



Within this embodiment, preferably R^9 is methyl, ethyl, or benzyl. Preferably R^{17} is H.

Within this embodiment, a specific compound of the present invention is 2-ethoxy-3-[6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridin-3-yl]propanoic acid or the pharmaceutically acceptable salts thereof.

Within this embodiment, a specific compound of the present invention is 2-methoxy-3-(6-{2-[5-methyl-2-(3-methylphenyl)-1,3-oxazol-4-yl]ethoxy}pyridin-3-yl)propanoic acid or the pharmaceutically acceptable salts thereof.

Within this embodiment, a specific compound of the present invention is 2-methoxy-3-[6-[2-(4-phenoxyphenyl)ethoxy]pyridin-3-yl]propanoic acid or the pharmaceutically acceptable salts thereof.

Within this embodiment, a specific compound of the present invention is 2-ethoxy-3-[6-(2-{4-[(phenylsulfonyl)oxy]phenyl}ethoxy)pyridin-3-yl]propanoic acid or the pharmaceutically acceptable salts thereof.

Within this embodiment, a specific compound of the present invention is 2-Ethoxy-3-{5-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridin-2-yl}-propionic acid or the pharmaceutically acceptable salts thereof.

Within this embodiment, a specific compound of the present invention is 2-Methoxy-2-methyl-3-{6-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propoxy]-pyridin-3-yl}-propionic acid or the pharmaceutically acceptable salts thereof.

Within this embodiment, a specific compound of the present invention is 2-Methoxy-2-methyl-3-{5-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridin-2-yl}-propionic acid or the pharmaceutically acceptable salts thereof.

Within this embodiment, a specific compound of the present invention is 3-(6-[2-[2-(4-Chloro-phenyl)-5-methyl-oxazol-4-yl]-ethoxy}-pyridin-3-yl)-2-methoxy-2-methyl-propionic acid or the pharmaceutically acceptable salts thereof.

Within this embodiment, a specific compound of the present invention is 2-Methoxy-2-methyl-3-{6-[2-(5-methyl-2-phenyl oxazol-4-yl)-ethoxy]-pyridin-3-yl}-propionic acid or the pharmaceutically acceptable salts thereof.

Within this embodiment, a specific compound of the present invention is 2-Methoxy-3-(6-[2-[2-(3-methoxy-phenyl)-5-methyl-oxazol-4-yl]-ethoxy}-pyridin-3-yl)-2-methyl-propionic acid or the pharmaceutically acceptable salts thereof.

The present invention also provides a method of treating non-insulin dependent diabetes mellitus in a mammal comprising administering to the mammal in need thereof a therapeutically effective amount of a compound of Formula (I). In one embodiment, said mammal has an impaired glucose tolerance.

The present invention also provides a method of treating polycystic ovarian syndrome in a mammal comprising administering to the mammal in need thereof a therapeutically effective amount of a compound of Formula (I).

The present invention also provides a method of treating obesity in a mammal comprising administering to the mammal in need thereof a therapeutically effective amount of a compound of Formula (I).

The present invention also provides a method of reducing body weight in an obese mammal comprising administering to the mammal in need thereof a therapeutically effective amount of a compound of Formula (I).

The present invention also provides a method of treating hyperglycemia in a mammal comprising administering to the mammal in need thereof a therapeutically effective amount of a compound of Formula (I).

The present invention also provides a method of treating hyperlipidemia in a mammal comprising administering to the mammal in need thereof a therapeutically effective amount of a compound of Formula (I).

The present invention also provides a method of treating hypercholesteremia in a mammal comprising administering to the mammal in need thereof a therapeutically effective amount of a compound of Formula (I).

The present invention also provides a method of treating atherosclerosis in a mammal comprising administering to the mammal in need thereof a therapeutically effective amount of a compound of Formula (I).

The present invention also provides a method of treating hypertriglyceridemia in a mammal comprising administering to the mammal in need thereof a therapeutically effective amount of a compound of Formula (I).

The present invention also provides a method of treating hyperinsulinemia in a mammal comprising administering to the mammal in need thereof a therapeutically effective amount of a compound of Formula (I).

The present invention also provides a method of treating a patient suffering from abnormal insulin and/or evidence of glucose disorders associated with circulating glucocorticoids, growth hormone, catecholamines, glucagon, or parathyroid hormone, comprising administering to said patient a therapeutically effective amount of a compound of Formula (I).

The present invention also provides a method of treating insulin resistance syndrome in humans comprising administering to a patient in need of treatment a therapeutically effective amount of a compound of Formula (I).

The present invention also provides a method of treating PPAR-related disorders in humans comprising administering to a patient in need of treatment a therapeutically effective amount of a compound of Formula (I).

The present invention also provides a method of modulating PPAR activity in a mammal, comprising administering to a mammal a therapeutically effective amount of a compound of Formula (I).

The present invention also provides a method of lowering blood glucose in a mammal, comprising administering to a mammal an amount of a compound of Formula (I) effective to lower blood glucose levels.

The present invention also provides a method of modulating fat cell differentiation in a mammal, comprising administering to a mammal a therapeutically effective amount of a compound of Formula (I).

The present invention also provides a method of modulating processes mediated by PPAR in a mammal, comprising administering to a mammal a therapeutically effective amount of a compound of Formula (I).

The present invention also provides a method of increasing insulin sensitivity in mammals, comprising administering to a mammal a therapeutically effective amount of a compound of Formula (I).

The present invention also provides a method of treating metabolic syndromes selected from the group consisting of galactosemia, maple syrup urine disease, phenylketonuria, hypersarcosinemia, thymine uraciluria, sulfinuria, isovaleric acidemia, saccharopinuria, 4-hydroxybutyric aciduria, glucose-6-phosphate dehydrogenase deficiency, and pyruvate dehydrogenase deficiency.

The present invention also provides a composition comprising at least one modulator of PPAR of Formula (I) and a pharmaceutically acceptable carrier thereof. Exemplary pharmaceutically acceptable carriers include carriers suitable for oral, intravenous, subcutaneous, intramuscular, intracutaneous, and the like administration. Administration in the form of creams, lotions, tablets, dispersible powders, granules, syrups, elixirs, sterile aqueous or non-aqueous solutions, suspensions or emulsions, and the like, is contemplated.

The PPAR agonists of the present invention may be administered in combination with other agents such as α-glucosidase inhibitors, aldose reductase inhibitors, biguanide preparations, statin base compounds, squalene synthesis inhibitors, fibrate base compounds, LDL catabolism promoters and angiotensin-converting enzyme inhibitors.

In the above description, an α-glucosidase inhibitor is a medicament having action in inhibiting a digestive enzyme such as amylase, maltase, α-dextrinase or sucrase, thereby retarding the digestion of starch or sucrose. Examples of α-glucosidase inhibitors include acarbose, N-(1,3-dihydroxy-2-propyl)valiolamine (common name: voglibose) and miglitol.

In the above description, an aldose reductase inhibitor is a medicament which inhibits a rate-limiting enzyme of the first step of the polyol pathway, thereby inhibiting diabetic complications. Examples include tolrestat, epalrestat, 2,7-difluoro-spiro(9H-fluoren-9,4'-imidazolidine)-2',5'-dione (common name: imirestat), 3-[(4-bromo-2-fluorophenyl)methyl]-7-chloro-3,4-dihydro-2,4-dioxo-1(2H)-quinazolineacetic acid (common name: zenarestat), 6-fluoro-2,3-dihydro-2,5'-dioxo-spiro[4H-1-benzopyran-4,4'-imidazolidine]- 2-carboxamide (SNK-860), zopolrestat, sorbinil and 1-[(3-bromo-2-benzofuranyl)sulfonyl]-2,4-imidazolidinedione (M-16209).

In the above description, a biguanide preparation is a medicament having effects in anaerobic glycolysis promotion, insulin action reinforcement at the periphery, intestinal glucose absorption inhibition, hepatic gluconeogenesis inhibition and fatty-acid oxidation inhibition and examples include phenformin, metformin and buformin.

In the above description, a statin base compound is a medicament which inhibits hydroxymethylglutaryl CoA (HMG-CoA) reductase, thereby lowering the blood cholesterol level and examples include pravastatin and the sodium salt thereof, simvastatin, lovastatin, atorvastatin and fluvastatin.

In the above description, a squalene synthesis inhibitor is a medicament for inhibiting squalene synthesis, thereby lowering the blood cholesterol level and examples include monopotassium (S)-α-[bis(2,2-dimethyl-1-

oxopropoxy)methoxy]phosphinyl-3-phenoxybenzene-butanesulfonate (BMS-188494).

In the above description, a fibrate base compound is a medicament for inhibiting synthesis and secretion of triglycerides in the liver and activating lipoprotein lipase, thereby lowering the triglyceride level in the blood. Examples include bezafibrate, beclobrate, binifibrate, ciprofibrate, clinofibrate, clofibrate, clofibric acid, etofibrate, fenofibrate, gemfibrozil, nicofibrate, pirifibrate, ronifibrate, simfibrate and theofibrate.

In the above description, a LDL catabolism promoter is a medicament for increasing LDL (low-density lipoprotein) receptors, thereby lowering the blood cholesterol level and examples include compounds described in Japanese Patent Application Kokai Hei 7-316144 or salts thereof, more specifically, N-[2-[4-bis(4-fluorophenyl)methyl-1-piperazinyl]ethyl]-7,7-diphenyl-2,4,6- heptatrienoic amide.

The above-described statin base compounds, squalene synthesis inhibitors, fibrate base compounds and LDL catabolism promoters can be replaced with another chemical effective for lowering the blood cholesterol or triglyceride level. Examples of such a medicament include nicotinic acid derivative preparations such as nicomol and niceritrol; antioxidants such as probucol; and ion exchange resin preparations such as cholestyramine.

In the above description, an angiotensin-converting enzyme inhibitor is a medicament for inhibiting angiotensin-converting enzyme, thereby lowering the blood pressure and at the same time, partially lowering the blood sugar level of a patient suffering from diabetes. Examples include captopril, enalapril, alacepril, delapril, ramipril, lisinopril, imidapril, benazepril, ceronapril cilazapril, enalaprilat, fosinopril, moveltipril, perindopril, quinapril, spirapril, temocapril and trandolapril.

For the preparation of oral liquids, suitable carriers include emulsions, solutions, suspensions, syrups, and the like, optionally containing additives such as wetting agents, emulsifying and suspending agents, sweetening, flavoring and perfuming agents, and the like.

For the preparation of fluids for parenteral administration, suitable carriers include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized, for example, by filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by

heating the compositions. They can also be manufactured in the form of sterile water, or some other sterile injectable medium immediately before use.

Definitions

For purposes of the present invention, as described and claimed herein, the following terms are defined as follows:

The term "halo", as used herein, unless otherwise indicated, means fluoro, chloro, bromo or iodo. Preferred halo groups are fluoro, chloro and bromo.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight or branched moieties.

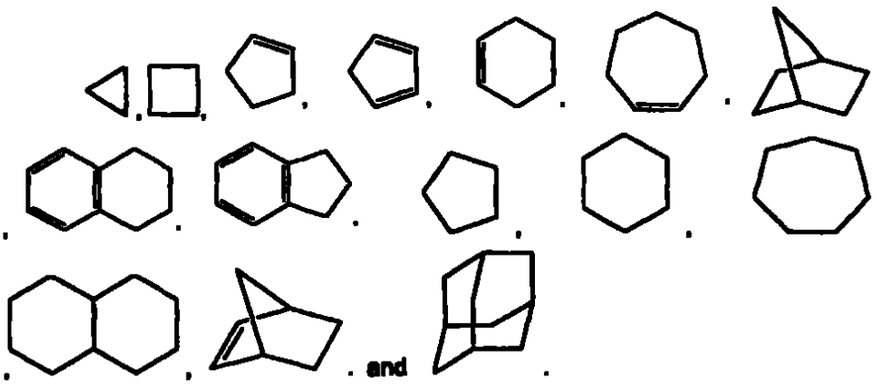
The term "alkenyl", as used herein, unless otherwise indicated, includes alkyl moieties having at least one carbon-carbon double bond wherein alkyl is as defined above and including E and Z isomers of said alkenyl moiety.

The term "alkynyl", as used herein, unless otherwise indicated, includes alkyl moieties having at least one carbon-carbon triple bond wherein alkyl is as defined above.

The term "alkoxy", as used herein, unless otherwise indicated, includes O-alkyl groups wherein alkyl is as defined above.

The term "Me" means methyl, "Et" means ethyl, and "Ac" means acetyl.

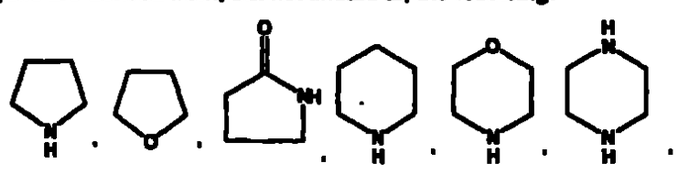
The term "cycloalkyl", as used herein, unless otherwise indicated refers to a non-aromatic, saturated or partially saturated, monocyclic or fused, spiro or unfused bicyclic or tricyclic hydrocarbon referred to herein containing a total of from 3 to 10 carbon atoms, preferably 5-8 ring carbon atoms. Exemplary cycloalkyls include monocyclic rings having from 3-7, preferably 3-6, carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Illustrative examples of cycloalkyl are derived from, but not limited to, the following:

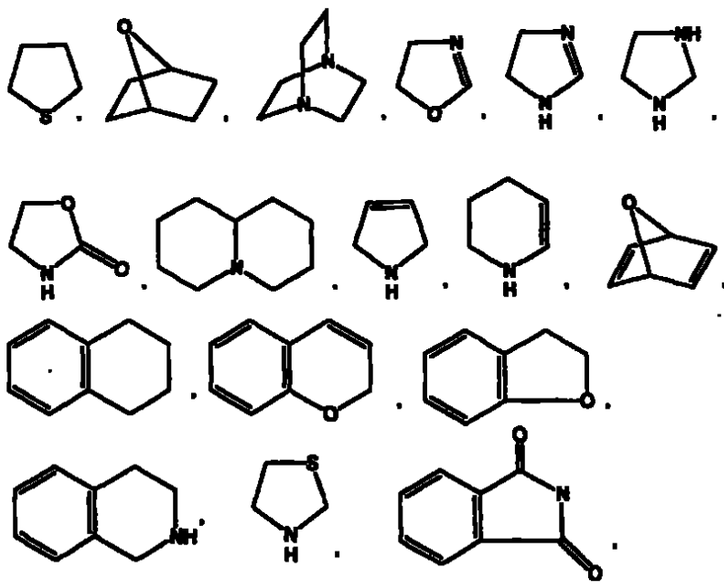


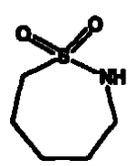
and

The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl or naphthyl.

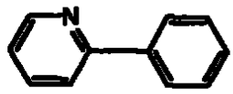
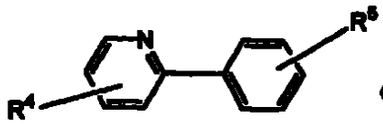
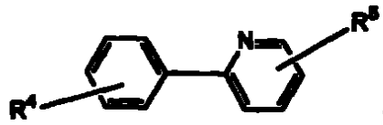
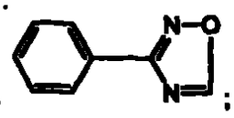
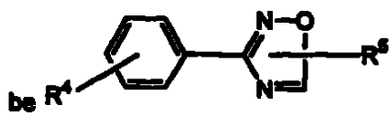
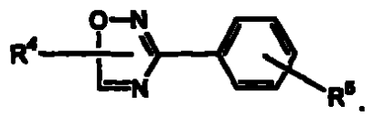
The term "4-10 membered heterocyclic", as used herein, unless otherwise indicated, includes aromatic and non-aromatic heterocyclic groups containing one to four heteroatoms each selected from O, S and N, wherein each heterocyclic group has from 4-10 atoms in its ring system, and with the proviso that the ring of said group does not contain two adjacent O or S atoms. Non-aromatic heterocyclic groups include groups having only 4 atoms in their ring system, but aromatic heterocyclic groups must have at least 5 atoms in their ring system. The heterocyclic groups include benzo-fused ring systems. An example of a 4 membered heterocyclic group is azetidinyl (derived from azetidine). An example of a 5 membered heterocyclic group is thiazolyl and an example of a 10 membered heterocyclic group is quinolinyl. Examples of non-aromatic heterocyclic groups are pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl and quinolizinyl. Examples of aromatic heterocyclic groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. The foregoing groups, as derived from the groups listed above, may be C-attached or N-attached where such is possible. For instance, a group derived from pyrrole may be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached). Further, a group derived from imidazole may be imidazol-1-yl (N-attached) or imidazol-3-yl (C-attached). The 4-10 membered heterocyclic may be optionally substituted on any ring carbon, sulfur, or nitrogen atom(s) by one to two oxo, per ring. An example of a heterocyclic group wherein 2 ring carbon atoms are substituted with oxo moieties is 1,1-dioxo-thiomorpholinyl. Other illustrative examples of 4-10 membered heterocyclic are derived from, but not limited to, the following:





and 

Unless otherwise indicated, the term "oxo" refers to =O.

The term "$-Ar^1-Ar^2-$", as used herein, unless otherwise indicated include two rings without any limitation of the order of attachments to R^4 and R^5. For example, if $-Ar^1-Ar^2-$ is defined as  ; then the $-Ar^1-Ar^2-$ groups can be  or  ; and if $-Ar^1-Ar^2-$ is defined as  ; then the $-Ar^1-Ar^2-$ groups can be  or  .

The phrase "pharmaceutically acceptable salt(s)", as used herein, unless otherwise indicated, includes salts of acidic or basic groups which may be present in

the compounds of formula (I). The compounds of formula (I) that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds of formula (I) are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, ethylsuccinate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodode, and valerate salts.

In the compounds of formula (I), where terms such as $(CR^{11}R^{12})_q$ or $(CR^{11}R^{12})_t$ are used, R^{11} and R^{12} may vary with each iteration of q or t above 1. For instance, where q or t is 2 the terms $(CR^{11}R^{12})_q$ or $(CR^{11}R^{12})_t$ may equal $-CH_2CH_2-$, or $-CH(CH_3)C(CH_2CH_3)(CH_2CH_2CH_3)-$, or any number of similar moieties falling within the scope of the definitions of R^{11} and R^{12}. Further, as noted above, any substituents comprising a CH_3 (methyl), CH_2 (methylene), or CH (methine) group which is not attached to a halogeno, SO or SO_2 group or to a N, O or S atom optionally bears on said group a substituent selected from hydroxy, C_1-C_4 alkoxy and amines.

The term "treating", as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, unless otherwise indicated, refers to the act of treating as "treating" is defined immediately above.

The term "modulate" or "modulating", as used herein, refers to the ability of a modulator for a member of the steroid/thyroid superfamily to either directly (by binding to the receptor as a ligand) or indirectly (as a precursor for a ligand or an inducer which promotes production of ligand from a precursor) induce expression of gene(s) maintained under hormone expression control, or to repress expression of gene(s) maintained under such control.

The term "obesity" or "obese", as used herein, refers generally to individuals who are at least about 20-30% over the average weight for his/her age, sex and height. Technically, "obese" is defined, for males, as individuals whose body mass index is greater than 27.8 kg/m, and for females, as individuals whose

body mass index is greater than 27.3 kg/m^2. Those of skill in the art readily recognize that the invention method is not limited to those who fall within the above criteria. Indeed, the method of the invention can also be advantageously practiced by individuals who fall outside of these traditional criteria, for example, by those who may be prone to obesity.

The term "inflammatory disorders", as used herein, refers to disorders such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, chondrocalcinosis, gout, inflammatory bowel disease, ulcerative colitis, Crohn's disease, fibromyalgia, and cachexia.

The phrase "therapeutically effective amount", as used herein, refers to that amount of drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal, or human that is being sought by a researcher, veterinarian, medical doctor or other.

The phrase "amount . . . effective to lower blood glucose levels," as used herein, refers to levels of compound sufficient to provide circulating concentrations high enough to accomplish the desired effect. Such a concentration typically falls in the range of about 10 nM up to 2 μM; with concentrations in the range of about 100 nM up to 500 nM being preferred. As noted previously, since the activity of different compounds which fall within the definition of Formula (I) as set forth above may vary considerably, and since individual subjects may present a wide variation in severity of symptoms, it is up to the practitioner to determine a subject's response to treatment and vary the dosages accordingly.

The phrase "insulin resistance", as used herein, refers to the reduced sensitivity to the actions of insulin in the whole body or individual tissues, such as skeletal muscle tissue, myocardial tissue, fat tissue or liver tissue. Insulin resistance occurs in many individuals with or without diabetes mellitus.

The phrase "insulin resistance syndrome", as used herein, refers to the cluster of manifestations that include insulin resistance, hyperinsulinemia, non insulin dependent diabetes mellitus (NIDDM), arterial hypertension, central (visceral) obesity, and dyslipidemia.

The phrase "in combination with", as used herein, means that the alpha substituted carboxylic acids compound of Formula (I) may be administered shortly before, shortly after, concurrently, or any combination of before, after, or concurrently, with such other agents as described in the previous paragraphs. Thus, the alpha substituted carboxylic acids compound of Formula (I) and the other agents may be administered simultaneously as either as a single composition or as two separate compositions or sequentially as two separate compositions.

Certain compounds of formula (I) may have asymmetric centers and therefore exist in different enantiomeric forms. All optical isomers and stereoisomers of the compounds of formula (I), and mixtures thereof, are considered to be within the scope of the invention. With respect to the compounds of formula (I), the invention includes the use of a racemate, one or more enantiomeric forms, one or more diastereomeric forms, or mixtures thereof. The compounds of formula (I) may also exist as tautomers. This invention relates to the use of all such tautomers and mixtures thereof.

Certain functional groups contained within the compounds of the present invention can be substituted for bioisosteric groups, that is, groups which have similar spatial or electronic requirements to the parent group, but exhibit differing or improved physicochemical or other properties. Suitable examples are well known to those of skill in the art, and include, but are not limited to moieties described in Patini, et al., *Chem. Rev*, 1996, 96, 3147-3176 and references cited therein.

The subject invention also includes isotopically-labelled compounds, which are identical to those recited in Formula (I), but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. Compounds of the present invention, prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labelled compounds of Formula (I) of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples and Preparations below, by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

This invention also encompasses pharmaceutical compositions containing and methods of treating bacterial infections through administering prodrugs of

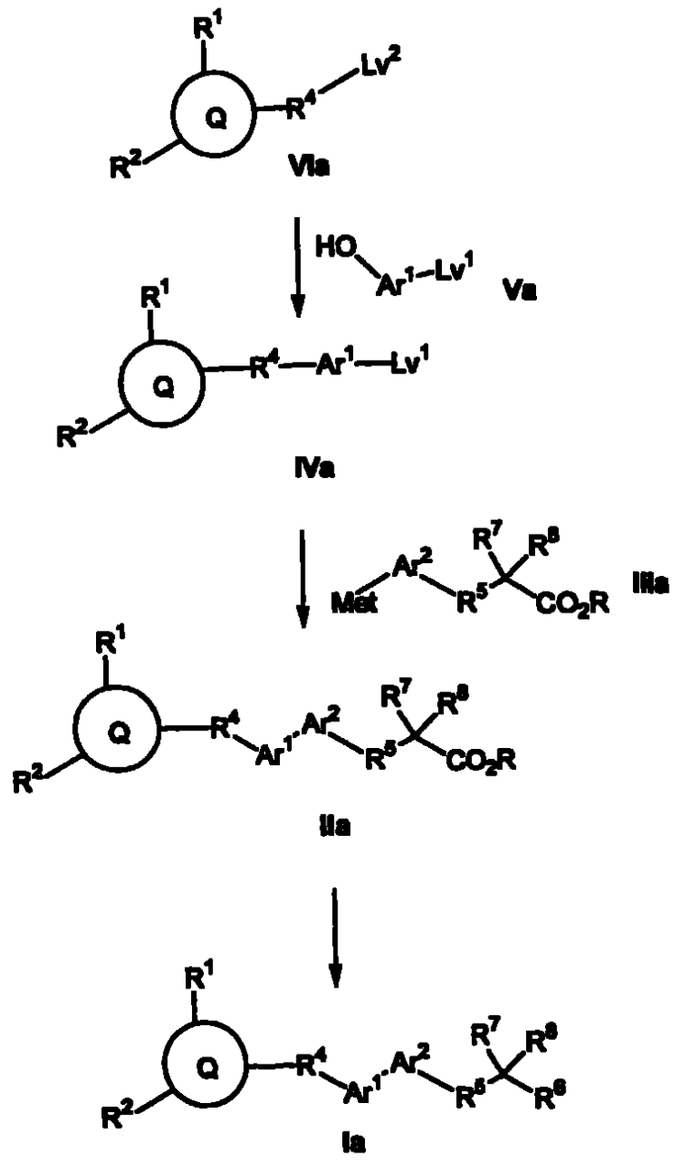
compounds of the formula 1. Compounds of formula 1 having free amino, amido, hydroxy or carboxylic groups can be converted into prodrugs. Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues is covalently joined through an amide or ester bond to a free amino, hydroxy or carboxylic acid group of compounds of formula 1. The amino acid residues include but are not limited to the 20 naturally occurring amino acids commonly designated by three letter symbols and also includes 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline homocysteine, homoserine, ornithine and methionine sulfone. Additional types of prodrugs are also encompassed. For instance, free carboxyl groups can be derivatized as amides or alkyl esters. Free hydroxy groups may be derivatized using groups including but not limited to hemisuccinates, phosphate esters, dimethylaminoacetates, and phosphoryloxymethyloxycarbonyls, as outlined in *Advanced Drug Delivery Reviews*, 1996, *19*, 115. Carbamate prodrugs of hydroxy and amino groups are also included, as are carbonate prodrugs, sulfonate esters and sulfate esters of hydroxy groups. Derivatization of hydroxy groups as (acyloxy)methyl and (acyloxy)ethyl ethers wherein the acyl group may be an alkyl ester, optionally substituted with groups including but not limited to ether, amine and carboxylic acid functionalities, or where the acyl group is an amino acid ester as described above, are also encompassed. Prodrugs of this type are described in *J. Med. Chem.*, 1996, 39, 10. Free amines can also be derivatized as amides, sulfonamides or phosphonamides. All of these prodrug moieties may incorporate groups including but not limited to ether, amine and carboxylic acid functionalities.

Other aspects, advantages, and preferred features of the invention will become apparent from the detailed description below.

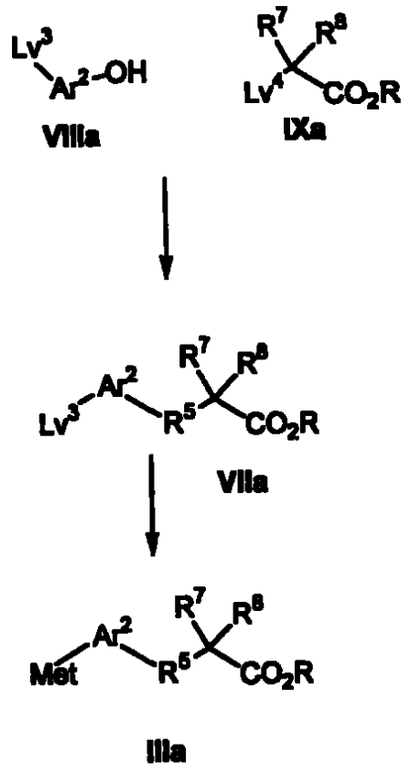
Detailed Description And Preferred Embodiments of The Invention

The following reaction Scheme illustrates the preparation of the compounds of the present invention. Unless otherwise indicated, R – R^{17}, Q, Y, Ar^1-Ar^4, and Ring A, in the reaction scheme and discussion that follow are as defined above.

Scheme 1

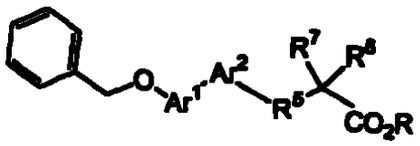

R1
Lv2
Q
R4
R2
VIa
HO
Ar1–Lv1
Va
R1
Q
R4—Ar1—Lv1
R2
IVa
R7
R8
Ar2
Met
R5
CO2R
IIIa
R1
Q
R4
Ar1-Ar2
R7
R8
R5
CO2R
R2
IIa
R1
Q
R4
Ar1-Ar2
R7
R8
R5
R6
R2
Ia

Scheme 2

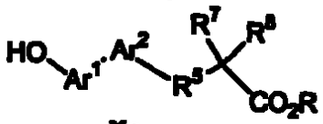

Lv3
Ar2-OH
VIIIa
R7
R8
Lv4
CO2R
IXa
Lv3
Ar2
R5
R7
R8
CO2R
VIIa
Met
Ar2
R5
R7
R8
CO2R
IIIa

5

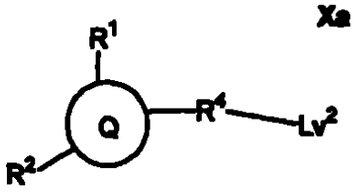
Scheme 3



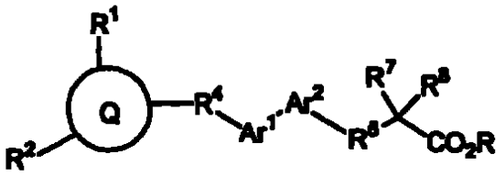
XIa



Xa

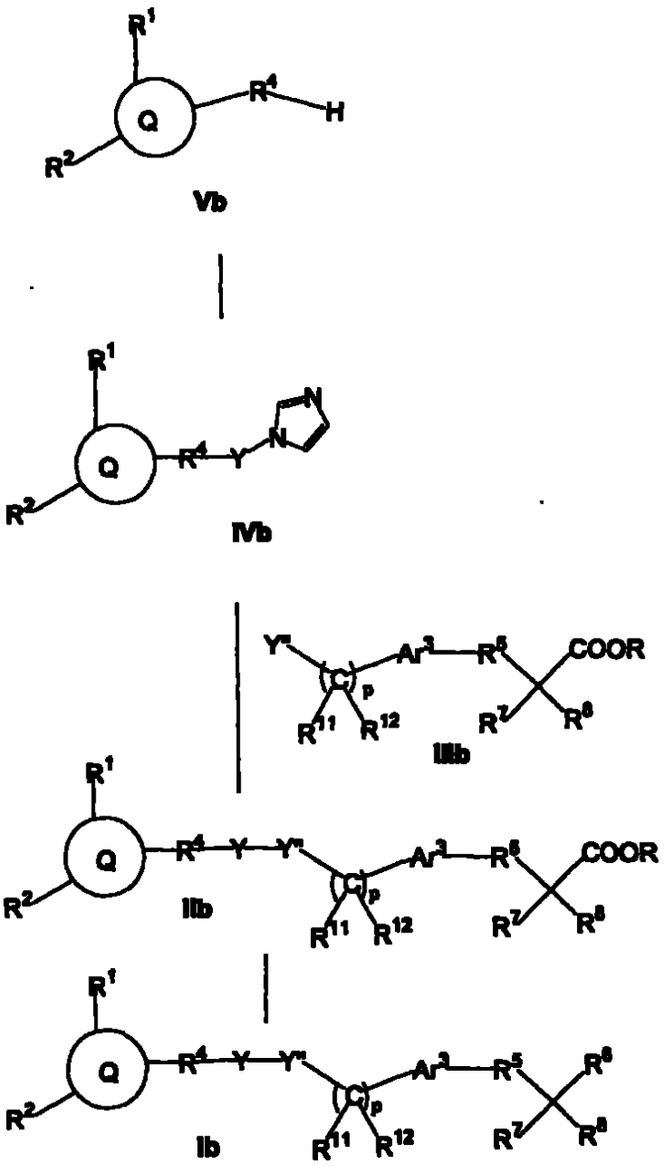


VIa



IIa

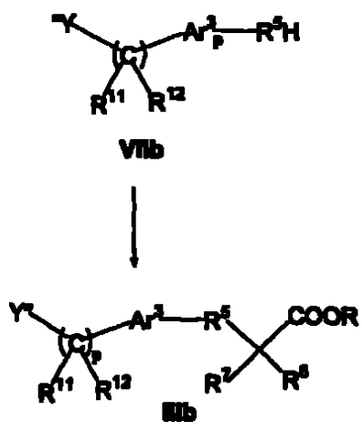
Scheme 4



R^5 is $-(CR^{11}R^{12})_m-Z-(CR^{11}R^{12})_s-$; wherein Z is -O-, $-NR^{10a}-$, or $-S(O)_j-$; wherein m and s are independently 0, 1, 2, or 3; and wherein j is 0, 1, or 2

5

Scheme 5

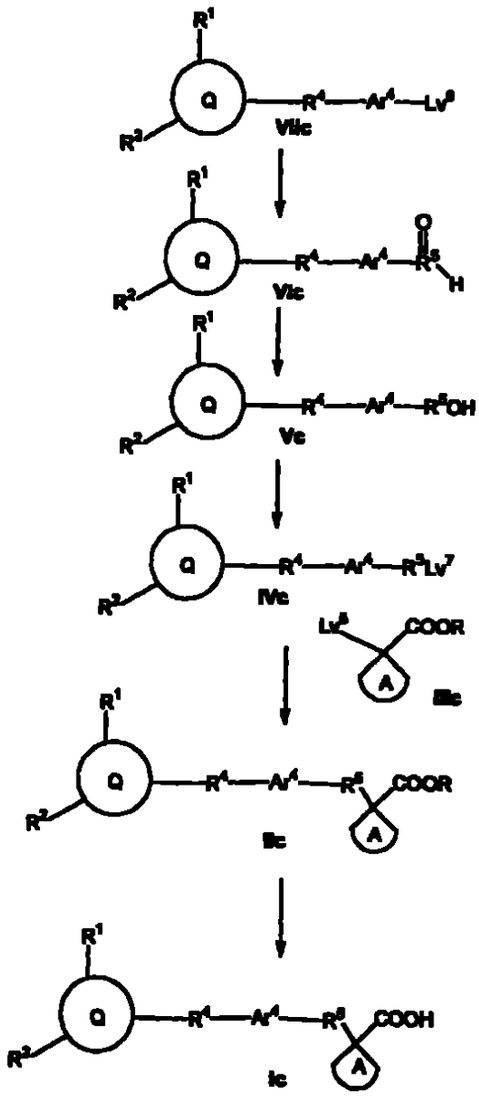


VIIb

IIIb

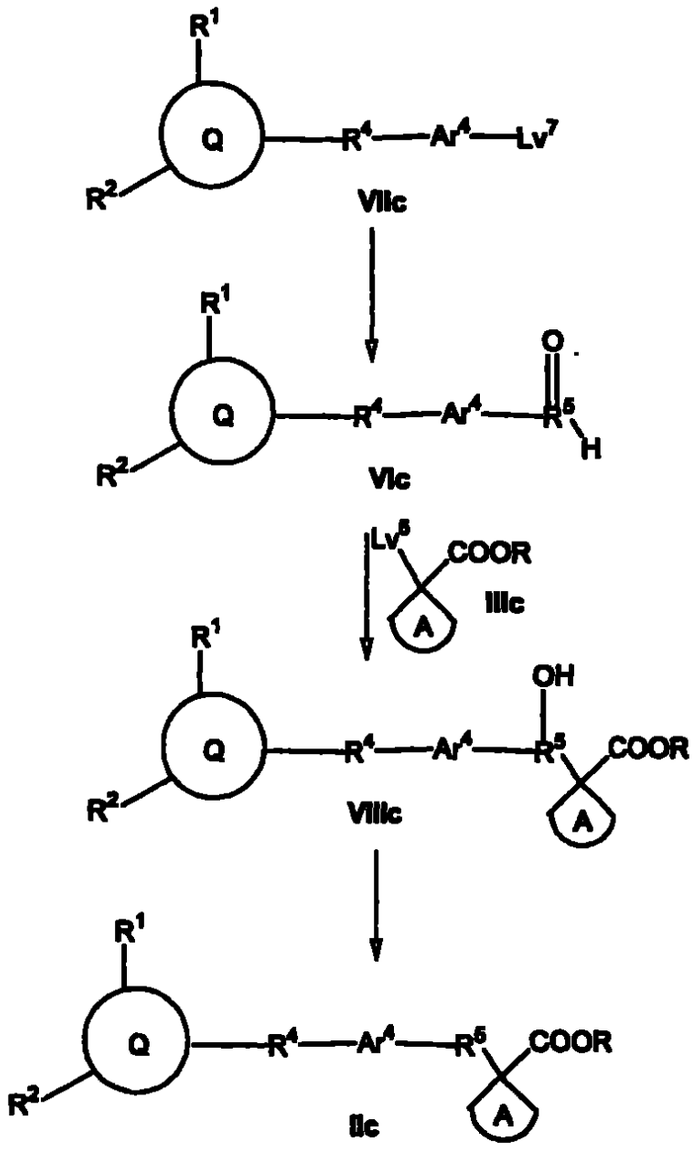
R^5 is $-(CR^{11}R^{12})_m-Z-(CR^{11}R^{12})_s$; wherein Z is -O-, $-NR^{10a}$-, or $-S(O)_j$-; wherein each m and s are independently 0, 1, 2, or 3; and wherein j is 0, 1, or 2

Scheme 6



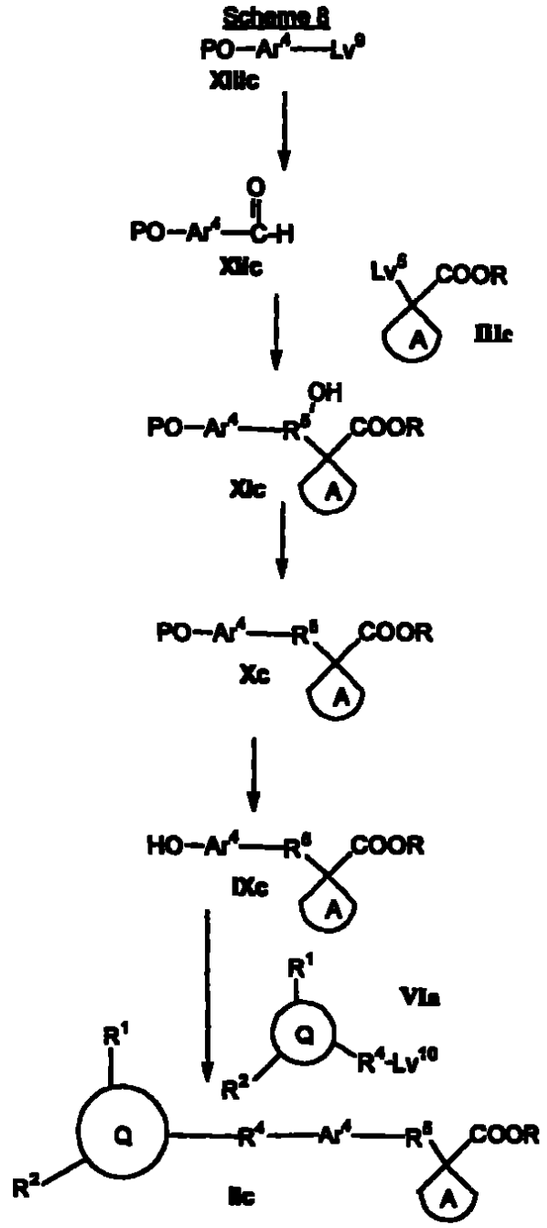
R^5 is $-(CR^{11}R^{12})_m-Z-(CR^{11}R^{12})_n-$ wherein Z is $-CH_2-$; wherein each m and n are independently 0, 1, 2, or 3.

Scheme 7



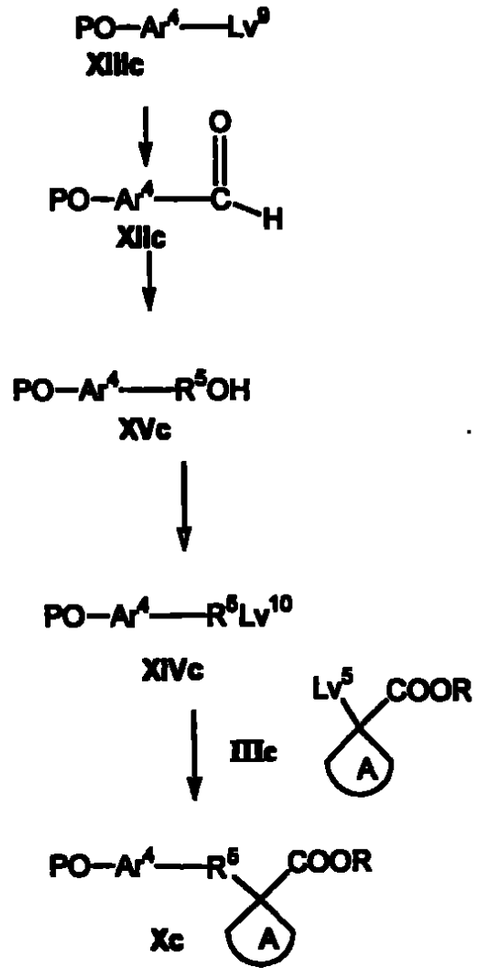
R^6 is $-(CR^{11}R^{12})_m-Z-(CR^{11}R^{12})_e-$; wherein Z is $-CH_2-$; wherein each m and e are independently 0, 1, 2, or 3.

Scheme 8



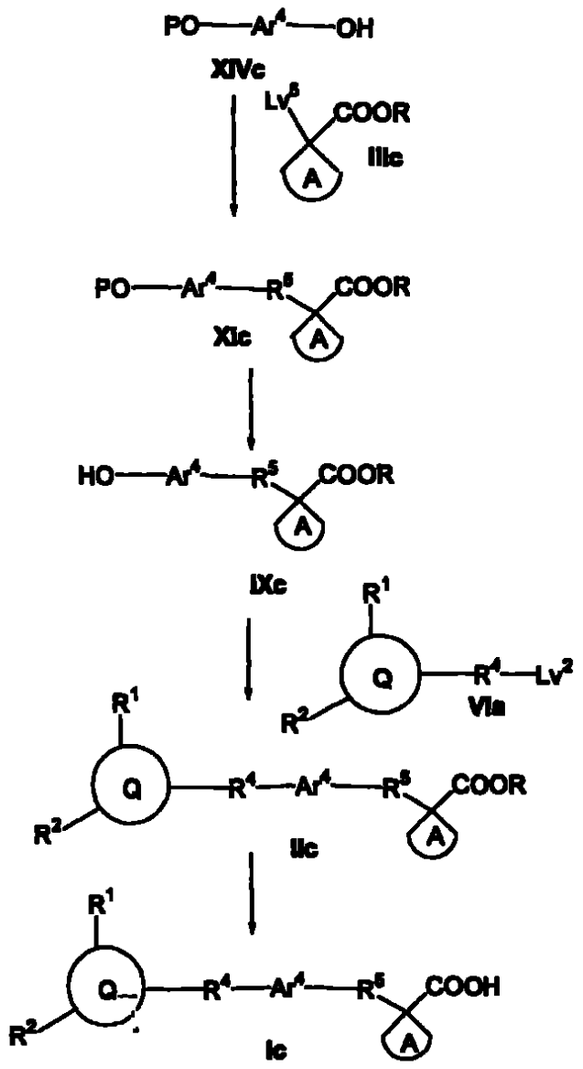
R^5 is $-(CR^{11}R^{12})_m-Z-(CR^{11}R^{12})_n-$; wherein Z is $-CH_2-$; wherein each m and n are independently 0, 1, 2, or 3.

Scheme 9



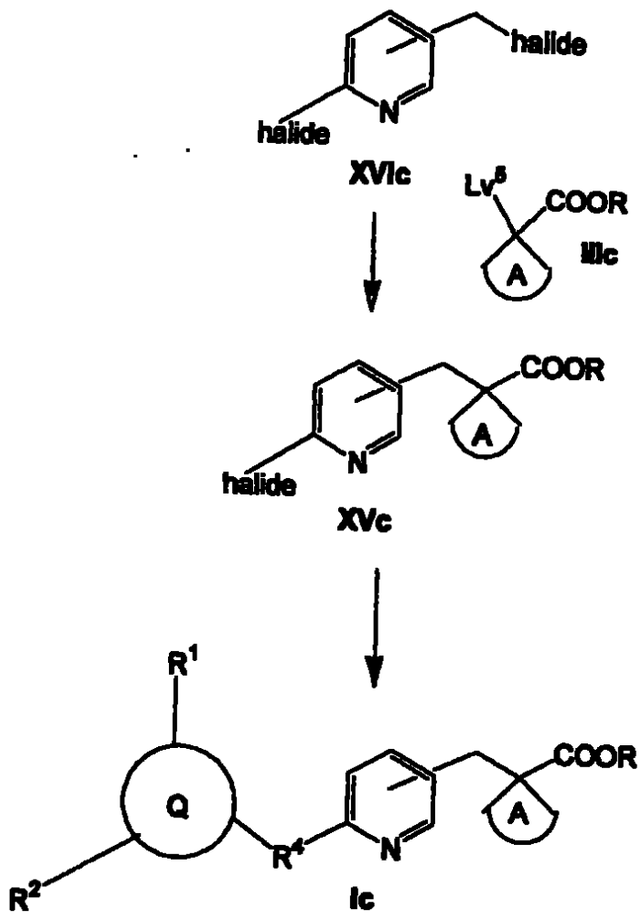
R^5 is $-(CR^{11}R^{12})_m-Z-(CR^{11}R^{12})_s$; wherein Z is $-CH_2-$; wherein each m and s are independently 0, 1, 2, or 3.

Scheme 10

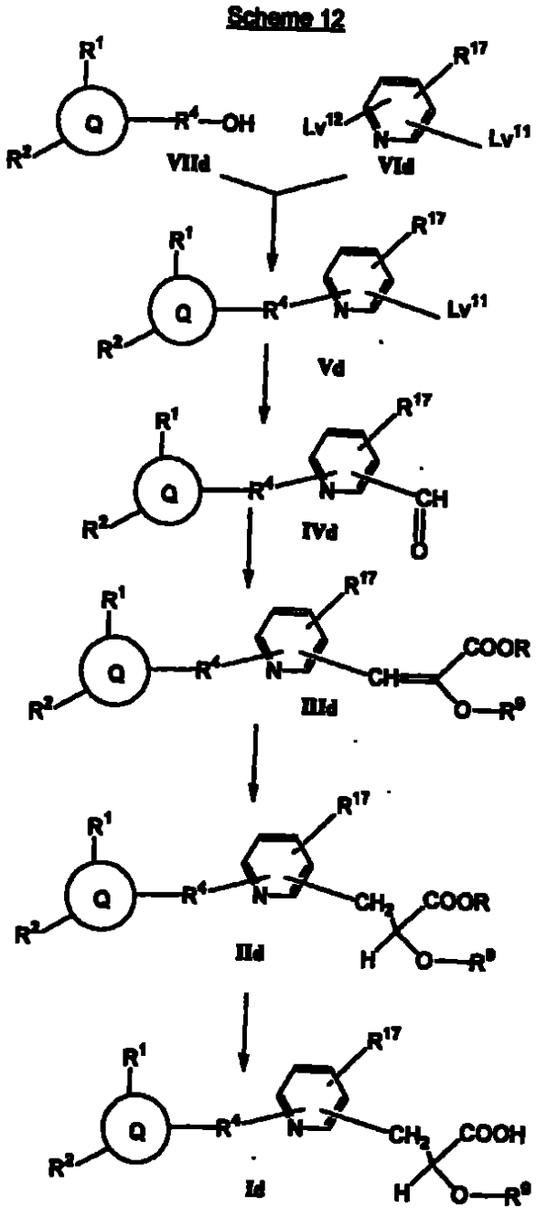


R^5 is $-(CR^{11}R^{12})_m-Z-(CR^{11}R^{12})_a-$; wherein Z is -O-, $-NR^{10a}-$, or $-S(O)_j-$; wherein each m and a are independently 0, 1, 2, or 3; and wherein j is 0, 1, or 2.

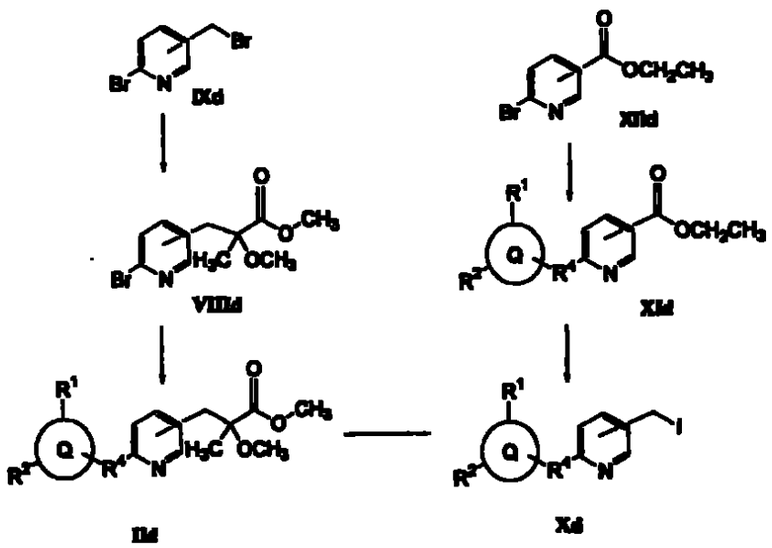
Scheme 11


halide
halide
N
XVIc
Lv5
COOR
A
IIIc
COOR
A
halide
N
XVc
R1
Q
R2
R4
N
COOR
A
Ic

Scheme 12


R1
Q
R2
R4—OH
VIIId
R17
Lv12
N
Lv11
VId
Vd
IVd
CH
O
IIId
COOR
O—R9
IId
CH2
H
Id
COOH

Scheme 13


Br
Br
N
IXd
O
OCH2CH3
Br
N
XIId
O
CH3
O
H3C
OCH3
Br
N
VIIId
R1
Q
R2
R4
O
OCH2CH3
N
XId
R1
Q
R2
R4
O
CH3
H3C
OCH3
N
IId
R1
Q
R2
R4
I
N
Xd

Referring to Scheme 1 above, the compound of formula Ia may be prepared by hydrolysis of compounds IIa, wherein the group CO_2R is a hydrolyzable ester group such as methyl ester (CO_2-CH_3) or ethyl ester (CO_2-CH_2CH_3), by alkali metal hydroxides (e.g. NaOH, LiOH, KOH) in a suitable solvent (e.g. aqueous THF, aqueous methanol or combinations thereof) at a temperature between 0 and 100 degrees or by heating in a microwave synthesizer. Compounds of formula IIa may be prepared by a coupling reaction of compound IVa, wherein Lv^1 is Cl, Br, I, or triflate, and an organometallic compound IIIa, wherein Met = boronic acid or ester, stannane etc, and the group CO_2R is as described above, mediated by a palladium(0) or other transition metal catalyst. Compound IVa can be obtained by alkylation of compound Va, wherein Lv^1 is as described above, with compound VIa, wherein Lv^2 is Cl, Br, I, or triflate.

Referring to Scheme 2 above, the compound of formula IIIa, which is used in Scheme 1, may be obtained from compounds VIIa, wherein Lv^3 is Cl, Br, I, or triflate, by palladium(0) mediated coupling reactions with a reagent such as pinacolatodiborane. Compounds VIIa, wherein Lv^3 is as described above, can be obtained by alkylation of compounds VIIIa, wherein Lv^3 is as described above, with compound IXa, wherein Lv^4 is Cl, Br, I, or triflate.

Referring to Scheme 3 above, esters IIa, which is used in Scheme 1, wherein the group CO_2R is as described above, may also be prepared by alkylation of compound Xa, wherein the group CO_2R is as described above, with compound VIa, wherein Lv^2 is as described above in the description of Scheme 1. Compounds Xa may be obtained from compound XIa, wherein the group CO_2R is as described above, by reacting compound XIa with a deprotecting agent, such as with hydrogen gas over a metal catalyst (e.g. palladium on carbon) in a suitable solvent (e.g. THF, methanol, ethanol) at a temperature between 0 degrees Celcius and 100 degrees Celcius.

Compounds XIa are commercially available or can be made by those skilled in the art.

Referring to Scheme 4 above, compounds of formula Ib; wherein R^5 is -$(CR^{11}R^{12})_m$-Z-$(CR^{11}R^{12})_n$; wherein Z is -O-, -NH^{10a}-, or -$S(O)_j$-; wherein each m and s are independently 0, 1, 2, or 3; and wherein j is 0, 1, or 2; may be prepared by hydrolysis of compounds IIIb, wherein R^5 is as described in the compounds of formula Ib and the group CO_2R is as described above, by an alkali metal hydroxide (e.g. Na OH, LiOH, KOH) in a suitable solvent (e.g. aqueous THF, aqueous methanol or combinations thereof) at a temperature 0 degrees Celcius and 100 degrees Celcius. Compounds of formula IIIb, wherein R^5 is as described in the compounds of formula Ib, may be prepared by reaction of compounds IIIIb, wherein

R^5 is as described in the compounds of formula IIb and the group CO_2R is as described above, with an activated acylating agent such as VIb in a suitable solvent (e.g. THF, acetonitrile, dioxane, toluene) at a temperature between 0 degrees Celcius and 100 degrees Celcius. Compounds IVb may be obtained from compound Vb by reacting compound Vb with compound VIb, wherein Lv^6 is a leaving group. Suitable compound VIb includes N,N'-carbonyl diimidazole.

Compounds Vb and VIb are commercially available or can be made by those skilled in the art.

Referring to Scheme 5 above, compounds of formula IIIb, which is used in Scheme 4, wherein R^5 is as described in the description of Scheme 4 and the group CO_2R is as described above, may be prepared by reacting compound VIIb wherein R^5 is as described in the previous paragraph, with an appropriate electrophile of formula Lv^6-$C(R^7R^8)$-COOR, wherein Lv^6 is a leaving group such as halo, in the presence of a base (e.g. cesium carbonate, potassium carbonate) in a suitable solvent (e.g. THF, DMF, acetonitrile, or DMSO) at a temperature between 0 degrees Celcius and 100 degrees Celcius. Suitable electrophiles of formula Lv^6-$C(R^7R^8)$-COOR include methyl 2-bromo-2-methyl propanoate. Compounds VIIb are commercially available or can be made by those skilled in the art.

Compounds of formula Ib, IIb, IIIb, and VIIb; wherein R^5 is -$(CR^{11}R^{12})_m$-Z-$(CR^{11}R^{12})_s$; wherein Z is -CH_2-, and wherein each m and s are as described above; can be prepared by methods known to those skilled in the art.

Referring to Scheme 6 above, compounds of formula Ic, wherein R^5 is -$(CR^{11}R^{12})_m$-Z-$(CR^{11}R^{12})_s$; wherein Z is -CH_2-, may be prepared by hydrolysis of compounds IIc, wherein the group CO_2R is as described above, by alkali metal hydroxides (e.g. NaOH, LiOH, KOH) in a suitable solvent (e.g. aqueous THF, aqueous methanol or combinations thereof) at a temperature between 0 degrees Celcius and 100 degrees Celcius or by heating in a microwave synthesizer. Compounds IIc may be prepared by alkylation of compound IIIc, wherein Lv^5 is a leaving group, with compound IVc (when Lv^7 is iodide, bromide, chloride or other leaving group). Various methods can be used to effect this reaction, such as deprotonation of compound IIIc (Lv^5 = H) with a base e.g. sodium bis(trimethylsilyl)amide. Compounds IVc may be prepared from compounds Vc by reaction with a halogenation agent or halogenation system e.g. oxalyl chloride and dimethyl formamide or from another halide (e.g. reaction of compound IVc, Lv^7 = Cl with sodium iodide). Compounds Vc may be prepared from compounds VIc by reacting compounds VIIIc with a reducing agent, such as sodium borohydride. Compounds VIc may be obtained from compound VIIc (Lv^6 = Br or other halogen)

by metal-halogen exchange (e.g. with butyllithium) followed by reaction with dimethyl formamide.

Alternatively, referring to Scheme 7 above, compounds of formula IIc, wherein R^5 is $-(CR^{11}R^{12})_m-Z-(CR^{11}R^{12})_s$; wherein Z is $-CH_2-$, may be prepared by the reductive deoxygenation of compound VIIIc using a silane and an acid source, typically triethylsilane and trifluoroacetic acid. Compounds VIIIc may be obtained by addition of compound IIIc to compound VIc. Various methods can be used to effect this reaction, such as deprotonation of IIIc (Lv^5 = H) with a base e.g. lithium diisopropylamide, or Reformatsky type activation of IIIc (Lv^5 = Br) with a metal or metal salt (e.g. chromium(II) chloride). Compounds VIc may be obtained from compound VIIc (Lv^5 = Br or other halo) by metal-halogen exchange (e.g. with butyllithium) followed by reaction with dimethyl formamide.

Alternatively, referring to Scheme 8 above, compound IIc, wherein R^5 is $-(CR^{11}R^{12})_m-Z-(CR^{11}R^{12})_s$; wherein Z is $-CH_2-$, may be obtained by reaction of compounds IXc with suitable coupling partners of formula VIa. These reactions may be effected using electrophiles VIa (e.g. Lv^2 = halides, sulphonate esters) in the presence of a base (e.g. cesium carbonate) or with alcohols (Lv^2 = OH) under Mitsunobu-type conditions (e.g. triphenyl phosphine and diethylazodicarboxylate). Compounds IXc can be prepared by deprotection of protected compounds Xc. Suitable protecting groups can include allyl, benzyl etc. Deprotection of Xc (P^2 = allyl) can be achieved by exposure to a soluble transition metal (e.g. tetrakis(triphenylphosphine)palladium(0)) in the presence of a base e.g. morpholine.

Intermediates Xc-XIIIc may be prepared by the methods described in Scheme 6.

Alternatively, referring to Scheme 9 above, compound Xc can be prepared by reacting compound XIVc (e.g. Lv^{10} = halides, sulphonate esters) with compound IIIc, wherein Lv^5 is as described above. Compound XIVc can be prepared by reacting compound XVc with $(C=O)Cl_2$ in a polar aprotic solvents such as dimethylformamide. Compound XVc can be prepared by reacting compound XIIIc with a reducing agent, such as sodium borohydride. Compounds XIIIc may be prepared by the method described in Scheme 6.

Alternatively, referring to Scheme 10 above, the compound of formula Ic, wherein R^5 is $-(CR^{11}R^{12})_m-Z-(CR^{11}R^{12})_s$; wherein Z is $-O-$, $-NR^{10a}-$, or $-S(O)_j-$; wherein each m and s are independently 0, 1, 2, or 3; and wherein j is 0, 1, or 2; may be prepared by hydrolysis of compounds IIc by alkali metal hydroxides (e.g. NaOH, LiOH, KOH) in a suitable solvent (e.g. aqueous THF, aqueous methanol or combinations thereof) at a temperature between 0 degrees Celcius and 100

degrees Celcius or by heating in a microwave synthesizer. Compounds of formula IIc may be obtained by reaction of compounds IXc with suitable coupling partners. These reactions may be effected using electrophiles (e.g. VIa; Lv^2 = halides, sulphonate esters) in the presence of a base (e.g. cesium carbonate, potassium carbonate or potassium *t*-butoxide) or with alcohols (VIa; Lv^2 = OH) under Mitsunobu-type conditions (e.g. triphenyl phosphine and diethylazodicarboxylate). Compounds IXc may be prepared by deprotection of compounds XIc wherein P is a protecting group. Suitable P protecting groups can include allyl, benzyl etc. Deprotection of XIc (P = allyl) can be achieved by exposure to a soluble transition metal (e.g. tetrakis(triphenylphosphine)palladium(0)) in the presence of a base e.g. morpholine or by reduction (XIc; P = benzyl) with hydrogen gas over a metal catalyst (e.g. palladium on carbon) in a suitable solvent (e.g. THF, methanol, ethanol) at a temperature between 0 degrees Celcius and 100 degrees Celcius. Compounds XIc can be obtained by alkylation of compounds XIVc with compound IIIc (Lv^1= Cl, Br, I, triflate, as described above).

Referring to Scheme 11 above, in certain cases alkylation of an enolate anion of compound IIIc with a benzylhalide having a formula XVIc affords compounds XVc. Compounds XVc can be converted into compounds Ic by e.g. palladium mediated coupling reaction in a solvent known by those skilled in the art (e.g., March, Advanced organic Chemistry, Fourth Edition).

Referring to Scheme 12 above, compounds of formula Id may be prepared by hydrolysis of compounds IId by alkali metal hydroxides (e.g. NaOH, LiOH, KOH) in a suitable solvent (e.g. aqueous THF, aqueous methanol or combinations thereof) at a temperature between 0 degrees Celcius and 100 degrees Celcius. Compounds of formula IId may be prepared by reaction of compounds IIId with an appropriate hydrogenation agent such as hydrogen gas over a metal catalyst (e.g., palladium on carbon) in a suitable solvent (e.g. THF, methanol, ethanol) at a temperature between 0 degrees Celcius and 100 degrees Celcius. Compounds of formula IIId may be prepared by reaction of compounds IVd with an appropriate triphenyl phosphine reagent having a formula: $(C_6H_5)_3P^+$-CH(OR^5)(COOR) Cl^- in a Wittig reaction. Suitable triphenyl phosphine reagents include 1,2-diethoxy-2-oxoethyl)(triphenyl) phosphonium chloride. Compounds of formula IVd may be prepared by reaction of compounds Vd as described in Scheme 9. Compounds of formula Vd may be prepared by reaction of compounds VId and VIId as described in Scheme 9.

Alternatively, compounds of formula IId may be prepared by the methods of Scheme 13. Referring to Scheme 13, alkylation of enolate anion of methyl 2-methoxy propanoate with a benzyl halide IXd affords compounds VIIId.

Compounds VIIId can be elaborated to compounds IId by e.g. palladium mediated coupling reaction. Compounds IId may also be prepared from compounds Xd. Compounds Xd can be prepared from compounds XIId by a sequence of reactions such as (i) palladium mediated coupling reaction to form compounds XId, and (ii) reduction of the ester to alcohol, and (iii) halide formation to form compounds IId.

Any of the above compounds of formula I and any of the compounds in the schemes 1-13 above can be converted into another analogous compound by standard chemical manipulations. These chemical manipulations are known to those skilled in the art and include a) removal of a protecting group by methods outlined in T. W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis", Second Edition, John Wiley and Sons, New York, 1991; b) displacement of a leaving group (halide, mesylate, tosylate, etc) with a primary or secondary amine, thiol or alcohol to form a secondary or tertiary amine, thioether or ether, respectively; c) treatment of phenyl (or substituted phenyl) carbamates with primary of secondary amines to form the corresponding ureas as in Thavonekham, B et. al. Synthesis (1997), 10, p1189; d) reduction of propargyl or homopropargyl alcohols or N-BOC protected primary amines to the corresponding E-allylic or E-homoallylic derivatives by treatment with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) as in Denmark, S. E.; Jones, T. K. J. Org. Chem. (1982) 47, 4595-4597 or van Benthem, R. A. T. M.; Michels, J. J.; Speckamp, W. N. Synlett (1994), 369-370; e) reduction of alkynes to the corresponding Z-alkene derivatives by treatment hydrogen gas and a Pd catalyst as in Tomassy, B. et. al. Synth. Commun. (1998), 28, p1201 f) treatment of primary and secondary amines with an isocyanate, acid chloride (or other activated carboxylic acid derivative), alkyl/aryl chloroformate or sulfonyl chloride to provide the corresponding urea, amide, carbamate or sulfonamide; g) reductive amination of a primary or secondary amine using $R^1CH(O)$; and h) treatment of alcohols with an isocyanate, acid chloride (or other activated carboxylic acid derivative), alkyl/aryl chloroformate or sulfonyl chloride to provide the corresponding carbamate, ester, carbonate or sulfonic acid ester.

The compounds of the present invention may have asymmetric carbon atoms. Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods known to those skilled in the art, for example, by chromatography or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixtures into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., alcohol), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers; or by chromatographic separation using chiral stationary or mobile phase. All such isomers, including

diastereomeric mixtures and pure enantiomers are considered as part of the invention.

The compounds of formulas (I) that are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate the compound of formula (I) from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is readily obtained. The desired acid salt can also be precipitated from a solution of the free base in an organic solvent by adding to the solution an appropriate mineral or organic acid.

Those compounds of formula (I) that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the acidic compounds of formula (I). Such non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium calcium and magnesium, etc. These salts can easily be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum yields of the desired final product.

The compounds of the present invention are modulators of PPAR, preferably PPAR γ and α. The compounds of the present invention can modulate processes mediated by PPAR-γ, which refers to biological, physiological, endocrinological, and other bodily processes which are mediated by receptor or receptor combinations which are responsive to the PPAR agonists described herein (e.g.,

diabetes, hyperlipidemia, obesity, impaired glucose tolerance, hypertension, fatty liver, diabetic complications (e.g. retinopathy, nephropathy, neurosis, cataracts and coronary artery diseases and the like), arteriosclerosis, pregnancy diabetes, polycystic ovary syndrome, cardiovascular diseases (e.g. ischemic heart disease and the like), cell injury (e.g. brain injury induced by strokes and the like) induced by atherosclerosis or ischemic heart disease, gout, inflammatory diseases (e.g. arthritis, pain, pyrexia, rheumatoid arthritis, inflammatory enteritis, acne, sunburn, psoriasis, eczema, allergosis, asthma, GI ulcer, cachexia, autoimmune diseases, pancreatitis and the like), cancer, osteoporosis and cataracts. Modulation of such processes can be accomplished in vitro or in vivo. In vivo modulation can be carried out in a wide range of subjects, such as, for example, humans, rodents, sheep, pigs, cows, and the like.

The compounds of the present invention may also be useful in the treatment of other metabolic syndromes associated with impaired glucose utilization and insulin resistance include major late-stage complications of NIDDM, such as diabetic angiopathy, atherosclerosis, diabetic nephropathy, diabetic neuropathy, and diabetic ocular complications such as retinopathy, cataract formation and glaucoma, and many other conditions linked to NIDDM, including dyslipidemia glucocorticoid induced insulin resistance, dyslipidemia, polycystic ovarian syndrome, obesity, hyperglycemia, hyperlipidemia, hypercholesteremia, hypertriglyceridemia, hyperinsulinemia, and hypertension. Brief definitions of these conditions are available in any medical dictionary, for instance, Stedman's Medical Dictionary (Xth Ed.).

The *in vitro* activity of the compounds of formula (I) may be determined by the following procedure.

Scintillation Proximity Assay (SPA) assays

In the SPA assay, 3H labeled darglitazone (for PPAR-γ) or GW2331 (for PPAR-α) is bound to the PPAR protein captured on SPA polylysine beads and generates radioactive count signal that can be detected by TopCounts (Packard). The PPAR-bound 3H labeled ligand can be displaced by an unlabeled compound. The KI of the compound can be then determined by the extent of displacement at various compound concentrations.

Reagents:

SPA polylysine beads, which can be purchased from Amersham Bioscience.

3H labeled Darglitazone for PPAR-γ.

3H labeled GW2331 for PPAR-α.

PPAR proteins.

Buffer – PBS, 10% glycerol, 14 mM beta-mercaptoethanol.

The compounds of the present invention that were tested all have Kis in at least one of the above SPA assays of between 0.3 nM to 30 μM. Certain preferred groups of compounds possess differential selectivity toward the various PPARs. One group of preferred compounds possesses selective activity towards PPAR-α over PPAR-γ. Another preferred group of compounds possesses selective activity towards towards PPAR-γ over PPAR-α. Another preferred group of compounds possesses selective activity towards both PPAR-α and PPAR-γ over PPAR-δ. Another preferred group of compounds possesses selective activity towards PPAR-δ over both PPAR-α and PPAR-γ.

The alpha substituted carboxylic acids compounds of Formula (I) may be provided in suitable topical, oral and parenteral pharmaceutical formulations for use in the treatment of PPAR mediated diseases. The compounds of the present invention may be administered orally as tablets or capsules, as oily or aqueous suspensions, lozenges, troches, powders, granules, emulsions, syrups or elixirs. The compositions for oral use may include one or more agents for flavoring, sweetening, coloring and preserving in order to produce pharmaceutically elegant and palatable preparations. Tablets may contain pharmaceutically acceptable excipients as an aid in the manufacture of such tablets. As is conventional in the art these tablets may be coated with a pharmaceutically acceptable enteric coating, such as glyceryl monostearate or glyceryl distearate, to delay disintegration and absorption in the gastrointestinal tract to provide a sustained action over a longer period.

Formulations for oral use may be in the form of hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin. They may also be in the form of soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions normally contain active ingredients in admixture with excipients suitable for the manufacture of an aqueous suspension. Such excipients may be a suspending agent, such as sodium carboxymethyl cellulose, methyl cellulose, hydroxypropylmethyl cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; a dispersing or wetting agent that may be a naturally occuring phosphatide such as lecithin, a condensation product of ethylene oxide and a long chain fatty acid, for example polyoxyethylene stearate, a condensation product of ethylene oxide and a long chain aliphatic alcohol such as heptadecaethyleneoxycetanol, a condensation product of ethylene oxide and a partial ester derived from a fatty acid and hexitol such as polyoxyethylene sorbitol

monooleate or a fatty acid hexitol anhydrides such as polyoxyethylene sorbitan monooleate.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to know methods using those suitable dispersing or wetting agents and suspending agents that have been mentioned above. The sterile injectable preparation may also be formulated as a suspension in a non toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the accetable vehicles and solvents that may be employed are water, Ringers solution and isotonic sodium chloride solution. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition fatty acids such as oleic acid find use in the preparation of injectables.

The alpha substituted carboxylic acids compounds of Formula (I) may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at about room temperature but liquid at rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and other glycerides.

For topical use preparations, for example, creams, ointments, jellies solutions, or suspensions, containing the compounds of the present invention are employed.

The alpha substituted carboxylic acids compounds of Formula (I) may also be administered in the form of liposome delivery systems such as small unilamellar vesicles, large unilamellar vesicles and multimellar vesicles. Liposomes can be formed from a variety of phospholipides, such as cholesterol, stearylamine or phosphatidylcholines.

Dosage levels of the compounds of the present invention are of the order of about 0.5 mg/kg body weight to about 100 mg/kg body weight. A preferred dosage rate is between about 30 mg/kg body weight to about 100 mg/kg body weight. It will be understood, however, that the specific dose level for any particular patient will depend upon a number of factors including the activity of the particular compound being administered, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy. To enhance the therapeutic activity of the present compounds they may be administered concomitantly with other orally active antidiabetic compounds such as the sulfonylureas, for example, tolbutamide and the like.

Methods of preparing various pharmaceutical compositions with a specific amount of active compound are known, or will be apparent, to those skilled in this art. For examples, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easter, Pa., 15th Edition (1975).

The examples and preparations provided below further illustrate and exemplify the compounds of the present invention and methods of preparing such compounds. It is to be understood that the scope of the present invention is not limited in any way by the scope of the following examples and preparations. In the following examples molecules with a single chiral center, unless otherwise noted, exist as a racemic mixture. Those molecules with two or more chiral centers, unless otherwise noted, exist as a racemic mixture of diastereomers. Single enantiomers/diastereomers may be obtained by methods known to those skilled in the art.

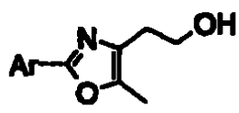
Where HPLC chromatography is referred to in the preparations and examples below, the general conditions used, unless otherwise indicated, are as follows. The column used is a ZORBAX™ RXC18 column (manufactured by Hewlett Packard) of 150 mm distance and 4.6 mm interior diameter. The samples are run on a Hewlett Packard- 1100 systemA gradient solvent method is used running 100 percent ammonium acetate / acetic acid buffer (0.2 M) to 100 percent acetonitrile over 10 minutes. The system then proceeds on a wash cycle with 100 percent acetonitrile for 1.5 minutes and then 100 percent buffer solution for 3 minutes. The flow rate over this period is a constant 3 ml / minute.

In the following examples and preparations, "Et" means ethyl, "Ac" means acetyl, "Me" means methyl, "ETOAC" or "ETOAc" means ethyl acetate, "THF" means tetrahydrofuran, and "Bu" means butyl.

Chiral supercritical fluid chromatography (SFC) conditions.

Single enantiomers of certain racemic compounds were obtained by SFC using a chiralpak AD-H column at 140 bar and 2.5 mL/min, chiralpak AS-H column at 140 bar and 2.5 mL/min, chiralpak OJ-H column at 140 bar and 2.5 mL/min.

Throughout the following sections, compounds of the general formula below were prepared by procedures analogous to those described in Heterocycles, 2001, 55(4), 689-703.



Example A-1

2-Methyl-2-[(3'-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-1,1'-biphenyl-3-yl)oxy]propanoic acid

To a solution of methyl 2-methyl-2-({3'-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-1,1'-biphenyl-3-yl}oxy)propanoate (0.89 g, 1.76 mmol) in methanol (20 mL) was added water (2.6 mL) and potassium carbonate (0.73 g, 2.0 equiv). The mixture was then heated at reflux for 5 hours and allowed to cool to ambient temperature. The solution was poured into water, acidified to pH 2 with 1N hydrochloric acid and extracted with ethyl acetate (3x30 mL). The combined organics were washed with saturated aqueous sodium chloride, dried (anhydrous sodium sulfate), filtered and concentrated to dryness to give the title compound as a white crystalline solid (0.6 g, 70%).

Elemental Analysis: Calcd for $C_{29}H_{27}NO_5$ C 73.51, H 5.95, N 3.06. Found:C 73.26, H 6.08, N 3.06.

LRMS: 458 $(M+H)^+$.

^1H NMR ($CDCl_3$, 400 MHz): 7.97 (2H, dd, J = 3.0, 6.6 Hz), 7.43 (2H, d, J = 2.8 Hz), 7.41 (1H, s), 7.31 (2H, t, J = 8.0 Hz), 7.23 (2H, d, J = 8.6 Hz), 7.17 (1H, d, J = 7.6 Hz), 7.12 (1H, bs), 6.93 (1H, dd, J = 1.4, 8.2 Hz), 6.87 (1H, dd, J = 2.0, 8.1 Hz), 4.29 (2H, t, J = 7.7 Hz), 3.07 (2H, t, J = 7.7 Hz), 2.40 (3H, s), 1.63 (6H, s).

Example A-2

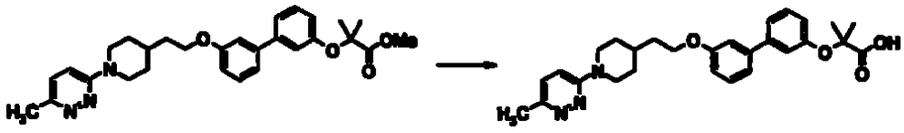
2-Methyl-2-[(3'-[[4-(trifluoromethyl)benzyl]oxy]-1,1'-biphenyl-3-yl)oxy]propanoic acid

Following the procedure described in Example A-1, starting from methyl 2-methyl-2-[(3'-[[4-(trifluoromethyl)benzyl]oxy]-1,1'-biphenyl-3-yl)oxy]propanoate, the title compound was produced.

LRMS: 431 $(M+H)^+$.

Example A-3

2-Methyl-2-[(3'-[2-[1-(6-methylpyridazin-3-yl)piperidin-4-yl]ethoxy]-1,1'-biphenyl-3-yl)oxy]propanoic acid



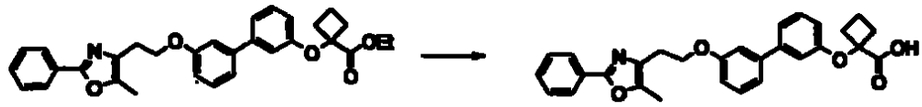
Following the procedure described in Example A-1, starting from methyl 2-methyl-2-[(3'-[2-[1-(6-methylpyridazin-3-yl)piperidin-4-yl]ethoxy]-1,1'-biphenyl-3-yl)oxy]propanoate, the title compound was produced as a pale yellow crystalline solid.

LRMS: 477 $(M+H)^+$.

^1H NMR ($CDCl_3$, 400 MHz): 7.27 (2H, q, J = 8.1 Hz), 7.20-7.18 (2H, m), 7.12 (1H, bd, J = 7.8 Hz), 7.08-7.06 (2H, m), 6.94-6.93 (1H, m), 6.91-6.90 (1H, m), 6.84 (1H, dd, J = 2.0, 7.8 Hz), 4.25 (2H, bd, J = 13.1 Hz), 4.04 (2H, t, J = 6.1 Hz), 2.88 (2H, t, J = 13.4 Hz), 2.48 (3H, s), 1.80-1.70 (5H, m), 1.65 (6H, s), 1.33-1.27 (2H, m).

Example A-4

1-({3'-[2-(5-Methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-1,1'-biphenyl-3-yl}oxy)cyclobutanecarboxylic acid



To a solution of ethyl 1-({3'-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-1,1'-biphenyl-3-yl}oxy)cyclobutanecarboxylate (0.138 g, 0.278 mmol) in tetrahydrofuran (3 mL) and methanol (1 mL) was added 2M aqueous lithium hydroxide (0.28 mL). The resulting mixture was stirred at ambient temperature for 16 hours. Water (5 mL) and diethyl ether (10 mL) were added and the resulting solution stirred for 10 min. The ethereal layer was removed and the aqueous layer acidified to pH 2 with 1N hydrochloric acid at 0 °C and stirred for 20 min. The white precipitate was collected by filtration and washed with ice-cold water. After drying at 40 °C under high vacuum the title compound was afforded as a white crystalline solid (0.091 g, 70%).

Elemental Analysis: Calcd for $C_{28}H_{27}NO_4 0.15LiCl$ C 73.18, H 5.72, N 2.94. Found:C 73.08, H 5.67, N 2.93.

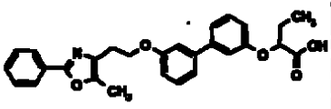
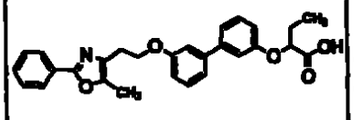
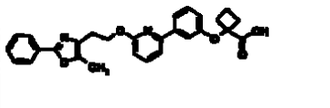
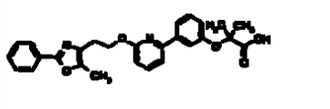
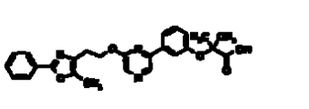
LRMS: 471 $(M+H)^+$.

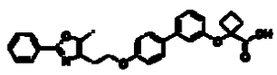
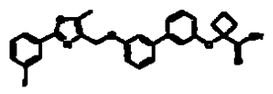
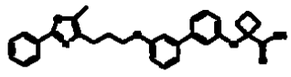
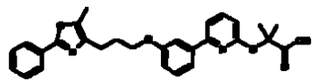
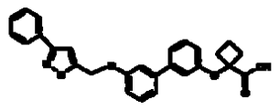
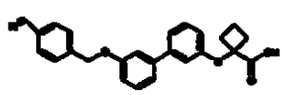
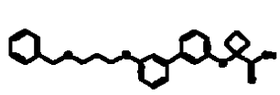
^1H NMR ($CDCl_3$, 400 MHz): 8.03-8.00 (2H, m), 7.43 (3H, t, J = 3.3 Hz), 7.30 (2H, t, J = 7.8 Hz), 7.16 (2H, d, J = 8.8 Hz), 7.09 (1H, t, J = 2.3 Hz), 6.91-6.85 (3H, m),

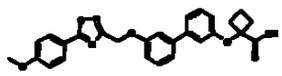
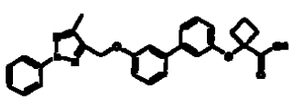
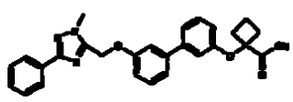
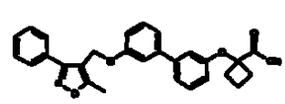
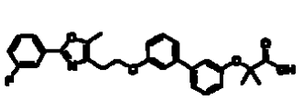
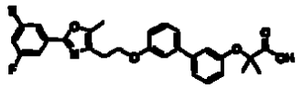
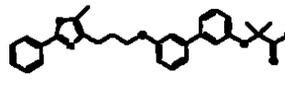
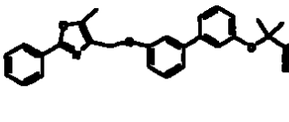
4.27 (2H, t, *J* = 7.8 Hz), 3.06 (3H, t, *J* = 8.1 Hz), 2.83-2.76 (2H, m), 2.53-2.46 (2H, m), 2.40 (3H, s), 2.06-1.97 (2H, m).

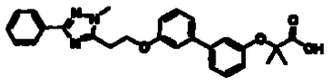
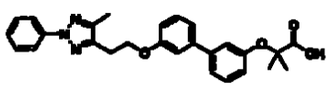
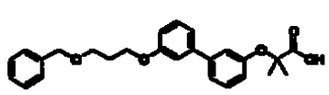
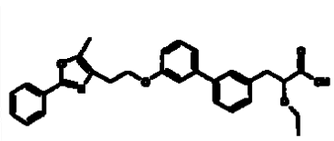
Examples A-5 to A-28

Examples A-5 to A-28 were prepared using procedures analogous to those described for Example A-4.

Ex. #	Structure	^{1}H NMR	MS (m/z) (LR or HR)	Analysis
A-5		($CDCl_3$, 400 MHz) 7.95 (2H, dd, *J* = 2.9, 6.7 Hz), 7.38-7.35 (3H, m), 7.29-7.22 (2H, m), 7.13-7.10 (3H, m), 7.07 (1H, t, *J* = 2.3 Hz), 6.91-6.88 (1H, m), 6.81 (1H, dd, *J* = 1.8, 8.3 Hz), 4.57 (1H, t, *J* = 6.2 Hz), 4.23 (2H, t, *J* = 7.7 Hz), 3.05-2.92 (2H, m), 2.34 (3H, s), 2.03-1.96 (2H, m), 1.06 (3H, t, *J* = 7.5 Hz).	for LR 458 $(M+H)^+$	Calcd for $C_{28}H_{27}NO_5 0.41H_2O$ C 72.34, H 6.03, N 3.01. Found:C 72.33, H 6.01, N 2.95.
A-6		(DMSO-d_6, 400 MHz) 7.91 (2H, dd, *J* = 1.8, 7.6 Hz), 7.73 (1H, t, *J* = 7.8 Hz), 7.52-7.44 (6H, m), 7.25 (1H, t, *J* = 8.0 Hz), 6.83 (1H, dd, *J* = 2.0, 8.1 Hz), 6.72 (1H, d, *J* = 8.1 Hz), 4.61 (2H, t, *J* = 6.7 Hz), 4.11 (1H, t, *J* = 6.3 Hz), 2.96 (2H, t, *J* = 6.7 Hz), 2.32 (3H, s), 1.84-1.69 (2H, m), 0.95 (3H, t, *J* = 7.3 Hz).	for LR 459 $(M+H)^+$	Calcd for $C_{27}H_{25}LiN_2O_5 2.32H_2O$ C 64.82, H 6.17, N 5.60. Found:C 64.83, H 5.89, N 5.52.
A-7		($CDCl_3$, 400 MHz) 8.02-8.00 (2H, m), 7.65-7.64 (1H, m), 7.61 (1H, m), 7.45-7.42 (3H, m), 7.40-7.30 (3H, m), 7.05 (1H, ddd, *J* = 1.0, 2.5, 7.8 Hz), 6.65 (1H, d, *J* = 8.1 Hz), 4.74-4.69 (2H, m), 3.10-3.07 (2H, m), 2.83-2.76 (2H, m), 2.47-2.38 (2H, m), 2.40 (3H, s), 2.09-1.95 (2H, m).	for LR 471 $(M+H)^+$	Calcd for $C_{28}H_{26}N_2O_5 0.09LiCl$ C 70.89, H 5.52, N 5.90. Found:C 70.94, H 5.65, N 5.93.
A-8		($CDCl_3$, 400 MHz) 8.11 (1H, dd, *J* = 1.5, 2.5 Hz), 8.00-7.97 (2H, m), 7.62 (1H, t, *J* = 7.6 Hz), 7.46-7.41 (4H, m), 7.35 (1H, d, *J* = 7.3 Hz), 7.31 (1H, t, *J* = 7.8 Hz), 7.00 (1H, ddd, *J* = 1.0, 2.8, 8.1 Hz), 6.65 (1H, d, *J* = 8.3 Hz), 4.74-4.69 (2H, m), 3.16-3.12 (2H, m), 2.41 (3H, s), 1.63 (6H, s).	for LR 459 $(M+H)^+$	
A-9		($CDCl_3$, 400 MHz) 8.63 (1H, bs), 8.13 (1H, bs), 8.06 (1H, dd, *J* = 1.3, 2.5 Hz), 7.99-7.96 (2H, m), 7.52 (1H, d, *J* = 7.8 Hz), 7.46-7.42 (3H, m), 7.35 (1H, t, *J* = 7.8 Hz), 7.04 (1H, dd, *J* = 2.3, 8.1 Hz), 4.72-4.68 (2H, m),	for LR 460 $(M+H)^+$	Calcd for $C_{28}H_{25}N_3O_5 0.47H_2O$ C 66.73, H 5.59, N 8.98. Found:C 66.69, H 5.48, N 8.96.

		3.16-3.12 (2H, m), 2.43 (3H, s), 1.63 (6H, s).		
A-10		^{1}H NMR (400 MHz, $CDCl_3$) 1.91 - 2.02 (m, 2 H), 2.24 - 2.31 (m, 3 H), 2.38 - 2.49 (m, 2 H), 2.75 (td, 2 H), 2.86 (t, 2 H), 4.04 (t, 2 H), 6.58 (dd, 1 H), 6.75 - 6.86 (m, 3 H), 7.04 (d, 1 H), 7.16 - 7.22 (m, 2 H), 7.30 - 7.38 (m, 3 H), 7.90 (dd, 2 H).	LRMS (*m/z*): 470 $(M+H)^+$.	
A-11		^{1}H NMR (400 MHz, $CDCl_3$) : 1.83-2.05(m, 2H), 2.51(s, 3H), 2.50-2.2.58(m, 2H), 2.75-2.83(m, 2H), 5.02(s, 2H), 6.52 (m, 1H), 6.96-7. 56(m, 9H), 7.73-7.86(m, 2H).		
A-12		^{1}H NMR (400 MHz, $CDCl_3$) : 1.97 - 2.07 (m, 2 H), 2.13 - 2.23 (m, 2 H), 2.29 (s, 3 H), 2.45 - 2.54 (m, 2 H), 2.70 - 2.81 (m, 4 H), 4.21 (q, 2 H), 6.63-6.65 (m, 1H), 7.07 - 7.18 (m, 2 H) 7.24 - 7.34 (m, 4 H) 7.37 - 7.45 (m, 4 H) 7.98 (dd, 2 H).	LRMS (*m/z*): 484.5 $(M+H)^+$.	
A-13		^{1}H NMR (400 MHz, $CDCl_3$) : 1.61 (s, 6 H), 2.35 (s, 3 H), 2.78 - 2.89 (m, 4 H), 4.23 - 4.31 (m, 2 H), 6.77 (d, 2 H), 7.15 (d, 4 H), 7.36 - 7.45 (m, 4 H), 7.97 (dd, 2 H).	LRMS (*m/z*): 473.5 $(M+H)^+$	
A-14		^{1}H NMR (400 MHz, $CDCl_3$) : 1.99 - 2.11 (m, 2 H), 2.51 (dq, 2 H), 2.77 - 2.85 (m, 2 H), 5.25 (s, 2 H), 6.65 - 6.72 (m, 2 H), 6.94 - 6.99 (m, 2 H), 7.15 - 7.22 (m, 2 H), 7.35 (t, 2 H), 7.42 - 7.51 (m, 2 H), 7.80 (dd, 4 H)	LRMS (*m/z*): 443.0 $(M+H)^+$.	
A-15		^{1}H NMR (400 MHz, $CDCl_3$) : 1.98 - 2.08 (m, 2 H), 2.45 - 2.55 (m, 2 H), 2.74 - 2.83 (m, 2 H), 5.18 (s, 2 H), 6.91 - 6.98 (m, 1 H) 7.13 - 7.21 (m, 2 H) 7.26 - 7.37 (m, 5 H), 7.56 - 7.63 (m, 2 H), 7.89 (d, 2 H).	LRMS (*m/z*): 423 $(M+H)^+$.	
A-16		^{1}H NMR (400 MHz, $CDCl_3$) : 1.96 - 2.07 (m, 2 H), 2.48-2.51(m, 2H), 2.73 - 2.82 (m, 2 H), 4.31 - 4.40 (m, 4 H), 6.63 (dd, 1 H), 6.92 - 7.00 (m, 5 H), 7.13 - 7.21 (m, 3 H), 7.25 - 7.36 (m, 4 H)	LRMS (*m/z*): 423 $(M+H)^+$.	

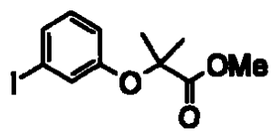
A-17		^{1}H NMR (400 MHz, $CDCl_3$) : 1.96 - 2.07 (m, 2 H), 2.44 - 2.55 (m, 2 H), 2.74 - 2.82 (m, 2 H), 3.89 (s, 1 H), 5.25 - 5.31 (s, 2 H), 6.63-6.65 (m, 1H), 7.00 - 7.10 (m, 4 H), 7.17 (t, 2 H), 7.23 - 7.31 (m, 4 H), 8.12 (d, 2 H).	LRMS (*m/z*): 473.5 $(M+H)^+$.	
A-18		^{1}H NMR (400 MHz, $CDCl_3$) : 2.02 - 2.14 (m, 2 H) 2.44 - 2.54 (m, 5H) 2.75 - 2.86 (m, 2 H) 5.26 (s, 2 H) 6.95 - 7.05 (m, 1 H) 7.16 - 7.23 (m, 2 H) 7.25 - 7.36 (m, 6 H) 7.46 (t, 2H) 8.02 (d, 2 H).	LRMS (*m/z*): 456.5 $(M+H)^+$.	
A-19		^{1}H NMR (400 MHz, $CDCl_3$) : 1.96 - 2.07 (m, 2 H), 2.44 - 2.54 (m, 5 H), 2.74 - 2.82 (m, 2 H), 5.25 (s, 2 H), 6.96 - 7.04 (m, 1 H), 7.16 (d, 2 H), 7.22 - 7.28 (m, 2 H), 7.32 (td, 4 H), 7.42 - 7.49 (m, 2 H), 7.99 - 8.05 (m, 2 H)	LRMS (*m/z*): 456.1 $(M+H)^+$.	
A-20		^{1}H NMR (400 MHz, $CDCl_3$) : 1.97 - 2.07 (m, 2 H), 2.52 (s, 3 H), 2.64 - 2.85 (m, 2 H), 2.74 - 2.82 (m, 2 H), 4.89 (s, 2H), 6.68-6.70 (m, 1H), 6.83-6.85 (m, 2H), 7.24 - 7.30 (m, 3 H) 7.41 - 7.47 (m, 3 H), 7.58-7.62(m, 2H), 7.66-7.68(m, 2H).	LRMS (*m/z*): 456.2 $(M+H)^+$	
A-21		^{1}H NMR (400 MHz, $CDCl_3$) 1.56 - 1.65 (m, 6 H), 2.43 (s, 3 H), 3.09 (t, 2 H), 4.33 (t, 2 H), 6.86 - 6.96 (m, 2 H), 7.11 - 7.19 (m, 2 H), 7.20 - 7.26 (m, 4 H), 7.32 (t, 2 H), 7.41 (td, 1 H), 7.70 (ddd, 1 H) 7.81 (d, 1 H).	LRMS (*m/z*): 476 $(M+H)^+$.	
A-22		^{1}H NMR (400 MHz, $CDCl_3$) 1.64 (s, 6 H), 2.41 (s, 3 H), 3.06 (t, 2 H), 4.31 (t, 2 H), 6.88 (dd, 3 H), 7.04 - 7.13 (m, 1 H), 7.14 - 7.23 (m, 2 H), 7.23 - 7.34 (m, 3 H), 7.52 (dd, 2 H).	LRMS (*m/z*): 494 $(M+H)^+$.	
A-23		^{1}H NMR (400 MHz, $CDCl_3$) : 1.71 (s, 6 H), 2.10 - 2.22 (m, 2 H), 2.35 (s, 3 H), 2.67 - 2.77 (m, 2 H), 3.99 - 4.09 (m, 2 H), 6.67-6.69(m, 2H), 7.04 - 7.13 (m, 2 H) 7.20 - 7.32 (m, 4 H) 7.37 - 7.44 (m, 2 H) 7.92 - 8.02 (m, 3H).	LRMS (*m/z*): 472.5 $(M+H)^+$	
A-24		^{1}H NMR (400 MHz, $CDCl_3$) : 1.76 (s, 6 H), 2.49 (s, 3 H), 5.16(s, 2H), 7.07 - 7.19 (m, 2 H), 7.23 (t, 1 H), 7.32 (td, 4 H), 7.36 - 7.47 (m, 4 H), 7.98 (dd, 2 H)	LRMS (*m/z*): 444.5 $(M+H)^+$	

A-25		^{1}H NMR (400 MHz, $CDCl_3$) 1.58 (s, 6 H), 3.35 (t, 2 H), 3.99 (s, 3 H), 4.40 (t, 2 H), 6.80 (d, 1 H), 6.81 (dd, 1 H), 7.00 (d, 1 H), 7.11 - 7.20 (m, 3 H), 7.25 (m, 2 H), 7.33 - 7.38 (m, 3 H), 7.92 - 8.00 (m, 2 H).	LRMS (*m/z*): 458 $(M+H)^+$.	
A-26		^{1}H NMR (400 MHz, $CDCl_3$) 1.56 (s, 6 H), 2.31 (s, 3 H), 3.11 (t, 2 H), 4.25 (t, 2 H), 6.81 (m, 2 H), 6.96 (s, 1 H), 7.06 (m, 2 H), 7.20 (m, 4 H), 7.30 (t, 2 H), 7.82 (d, 2 H).	LRMS (*m/z*): 458 $(M+H)^+$.	
A-27		^{1}H NMR (400 MHz, $CDCl_3$) 1.62 (s, 6 H), 2.07 - 2.15 (m, 2 H), 3.60 - 3.71 (m, 2 H), 4.13 (q, 2 H), 4.53 (s, 2 H), 6.83 - 6.93 (m, 2 H), 7.01 - 7.09 (m, 1 H), 7.12 (d, 1 H), 7.14 - 7.20 (m, 1 H), 7.30 (ddd, 8 H).	LRMS (*m/z*): 421 $(M+H)^+$.	
A-28		^{1}H NMR (400 MHz, $CDCl_3$) : 1.18 (t, 3 H), 2.43 (s, 3 H), 2.96 - 3.06 (m, 4 H), 3.32-3.35(m, 2H), 3.62-3.65(m, 1H), 4.24 - 4.33 (m, 2 H), 7.07 - 7.19 (m, 2 H), 7.23 (t, 1 H), 7.32 (td, 4 H), 7.36 - 7.47 (m, 4 H), 7.98 (dd, 2 H).	LRMS (*m/z*): 472.5 $(M+H)^+$.	

Preparations of Starting Materials for Examples A-1 to A-28 (Preparations a-1 to a-11)

Preparation a-1

Methyl 2-(3-Iodophenoxy)-2-methylpropanoate



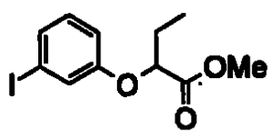
To a solution of 3-Iodophenol (1.08 g, 4.9 mmol) in *N,N*-dimethylformamide (10 mL) was added methyl 2-bromo-2-methyl-propionate (0.76 mL, 1.2 equiv) and cesium carbonate (3.45 g, 2 equiv). The resulting mixture was heated at 90 °C for 24 hours and then allowed to cool to ambient temperature. Water was introduced and the mixture extracted with diethyl ether (3x20 mL). The combined organics were washed with water and saturated aqueous sodium chloride, dried (anhydrous sodium sulfate), filtered and concentrated. The residue was purified by silica gel chromatography using 0-30% ethyl acetate in hexanes to provide the title compound (0.83 g, 53%).

LRMS: 321 $(M+H)^+$.

^{1}H NMR ($CDCl_3$, 400 MHz): 7.22 (1H, dt, J = 1.3, 7.8 Hz), 7.12 (1H, dd, J = 1.6, 2.4 Hz), 6.84 (1H, t, J = 8.1 Hz), 6.66 (1H, ddd, J = 0.8, 2.5, 8.3 Hz), 3.66 (3H, s), 1.47 (6H, s).

Preparation a-2

Methyl 2-(3-iodophenoxy)butanoate



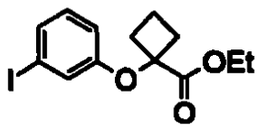
Following the procedure described in Preparation a-1, using ethyl 2-bromopropionate in place of methyl 2-bromo-2-methyl-propionate at ambient temperature, the title compound was obtained in 93% yield.

LRMS: 321 $(M+H)^+$.

^{1}H NMR ($CDCl_3$, 400 MHz): 7.30 (1H, ddd, J = 1.0, 1.5, 7.8 Hz), 7.24 (1H, dd, J = 1.6, 2.4 Hz), 6.97 (1H, dd, J = 7.8, 8.3 Hz), 6.82 (1H, ddd, J = 1.0, 2.5, 8.6 Hz), 4.53 (1H, dd, J = 5.8, 6.8 Hz), 3.75 (3H, s), 2.00-1.93 (2H, m), 1.05 (3H, t, J = 7.5 Hz).

Preparation a-3

Ethyl 1-(3-bromophenoxy)cyclobutanecarboxylate

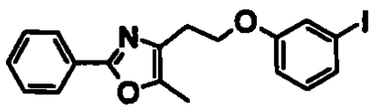


Following the procedure described in Preparation a-1, using 3-bromophenol and ethyl 1-bromocyclobutanecarboxylate as starting materials and heating in a solution of acetonitrile, the title compound was obtained in 56% yield.

LRMS: 300 $(M+H)^+$.

Preparation a-4

4-[2-(3-Iodophenoxy)ethyl]-5-methyl-2-phenyl-1,3-oxazole



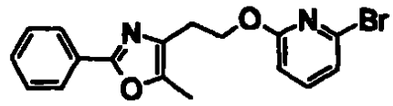
Following the procedure described in Preparation a-1, starting from 3-iodophenol and 2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)-ethyl-4-methylbenzenesulfonate at ambient temperature, the title compound was produced in 77% yield as a colorless oil.

LRMS: 406 $(M+H)^+$.

^{1}H NMR ($CDCl_3$, 400 MHz): 7.87 (2H, dd, J = 1.9, 7.7 Hz), 7.34-7.29 (3H, m), 7.15-7.13 (2H, m), 6.86 (1H, t, J = 8.1 Hz), 6.78-6.73 (1H, m), 4.10 (2H, t, J = 6.6 Hz), 2.85 (2H, t, J = 6.6 Hz), 2.26 (3H, s).

Preparation a-5

2-Bromo-6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridine



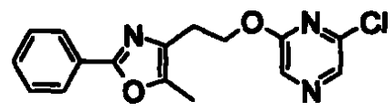
To a solution of 2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)-ethanol (1.04 g, 5.1 mmol) and 2,6-dibromopyridine (1.21 g, 5.1 mmol) in anhydrous dioxane (20 mL) at 0 °C was added sodium hydride (60% in oil, 0.368 g, 3 equiv). The resulting mixture was stirred at ambient temperature for 16 hours. The mixture was poured into ice-cold water and extracted with ethyl acetate (3x50 mL). The combined organics were washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride, dried (anhydrous sodium sulfate), filtered and concentrated. The residue was purified by silica gel chromatography using 0-50% ethyl acetate in hexanes to afford the title compound as a white crystalline solid (1.19 g, 65%).

LRMS: 359 $(M+H)^+$.

^{1}H NMR ($CDCl_3$, 400 MHz): 7.97 (2H, dd, J = 1.8, 7.8 Hz), 7.44-7.35 (4H, m), 7.03 (1H, d, J = 7.3 Hz), 6.65 (1H, d, J = 8.1 Hz), 4.55 (2H, t, J = 6.8 Hz), 2.97 (2H, t, J = 6.8 Hz), 2.34 (3H, s).

Preparation a-6

2-Chloro-6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyrazine



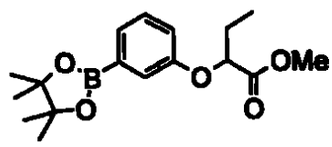
Following the procedure described in Preparation a-5, starting from 2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)-ethanol and 2,6 dichloropyrazine, the title compound was obtained in 64% yield.

LRMS: 316 $(M+H)^+$.

^{1}H NMR ($CDCl_3$, 400 MHz): 8.11 (2H, d, J = 10.4 Hz), 7.97 (2H, dd, J = 1.9, 7.7 Hz), 7.44-7.39 (3H, m), 4.60 (2H, t, J = 6.7 Hz), 2.99 (2H, t, J = 6.7 Hz), 2.35 (3H, s).

Preparation a-7

Methyl 2-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]butanoate



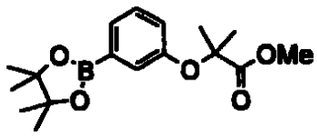
To a solution of methyl 2-(3-iodophenoxy)-2-methylpropanoate (Preparation a-2) (1.49 g, 4.65 mmol) in dimethylsulfoxide (40 mL) was added potassium acetate (1.37 g, 3 equiv), bis(pinacolato)diboron (1.3 g, 1.1 equiv) and a solution of [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium (II) complex (0.152 g, 0.04 equiv) in dichloromethane. The resulting mixture was heated at 80 °C for 16 hours and allowed to cool to ambient temperature. Water was introduced and the mixture extracted with diethyl ether (3x30 mL). The combined organics were washed with 5% aqueous sodium bicarbonate (2x50 mL) and saturated aqueous sodium chloride, dried (anhydrous sodium sulfate), filtered and concentrated. The residue was purified by silica gel chromatography using 0-25% ethyl acetate in hexanes to provide the title compound (0.92 g, 62%)

LRMS: 321 $(M+H)^+$.

^{1}H NMR ($CDCl_3$, 400 MHz): 7.40 (1H, d, J = 7.3 Hz), 7.32 (1H, d, J = 2.8 Hz), 7.28 (1H, d, J = 8.1 Hz), 6.97 (1H, ddd, J = 1.0, 2.8, 8.1 Hz), 4.64 (1H, t, J = 6.3 Hz), 3.73 (3H, s), 2.01-1.94 (2H, m), 1.32 (12H, s), 1.06 (3H, t, J = 7.5 Hz).

Preparation a-8

Methyl 2-methyl-2-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]propanoate



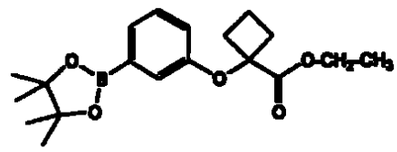
Following the procedure described in Preparation a-7, using methyl 2-(3-iodophenoxy)-2-methylpropanoate (Preparation 1) as starting material, the title compound was produced in 75% yield.

LRMS: 321 $(M+H)^+$.

^{1}H NMR ($CDCl_3$, 400 MHz): 7.42 (1H, d, J = 7.1 Hz), 7.29 (1H, d, J = 2.8 Hz), 7.22 (1H, t, J = 7.8 Hz), 6.90 (1H, ddd, J = 0.8, 2.8, 8.1 Hz), 3.75 (3H, s), 1.56 (6H, s), 1.30 (12H, s).

Preparation a-9

Ethyl 1-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]cyclobutanecarboxylate

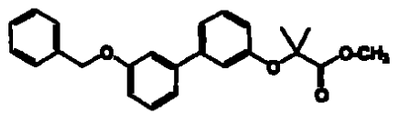


Following the procedure described in Preparation a-7, using ethyl 1-(3-bromophenoxy)cyclobutanecarboxylate (Preparation 3) as starting material, the title compound was produced in 80% yield.

LRMS: 347 $(M+H)^+$.

Preparation a-10

Methyl 2-[(3'-(benzyloxy)-1,1'-biphenyl-3-yl)oxy]-2-methylpropanoate



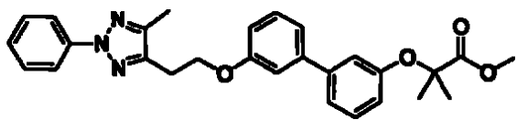
To a solution of methyl 2-(3-iodophenoxy)-2-methylpropanoate (Preparation a-1) (1.14 g, 3.56 mmol) in benzene (20 mL) was added 3-benzyloxyphenylboronic acid (0.89 g, 1.1 equiv), 2M aqueous sodium carbonate (3.56 mL) and tetrakis(triphenylphosphine) palladium (0) (0.2 g, 0.05 equiv). The resulting mixture heated at reflux for 2 hours and allowed to cool to ambient temperature. Water was added and the mixture extracted with diethyl ether (3x20 mL). The combined organics were washed with 5% aqueous sodium bicarbonate and saturated aqueous sodium chloride, dried (anhydrous sodium sulfate) and concentrated. The residue was purified by silica gel chromatography using 0-15% ethyl acetate in hexanes to give the title compound as a colorless oil (1.08 g, 81%).

LRMS: 377 $(M+H)^+$.

^{1}H NMR ($CDCl_3$, 400 MHz): 7.47-7.45 (2H, m), 7.39 (2H, t, J = 7.3 Hz), 7.33 (2H, t, J = 7.6 Hz), 7.28 (1H, t, J = 8.0 Hz), 7.21 (1H, ddd, J = 1.0, 1.5, 8.1 Hz), 7.17 (1H, dd, J = 1.8, 2.3 Hz), 7.14 (1H, dm, J = 7.6 Hz), 7.08 (1H, dd, J = 1.8, 2.3 Hz), 6.96 (1H, ddd, J = 0.8, 2.5, 8.3 Hz), 6.79 (1H, ddd, J = 1.0, 2.5, 8.1 Hz), 5.11 (2H, s), 3.78 (3H, s), 1.62 (6H, s).

Preparation a-11

Methyl 2-methyl-2-{[3'-[2-(5-methyl-2-phenyl-2*H*-1,2,3-triazol-4-yl)ethoxy]biphenyl-3-yl]oxy}propanoate



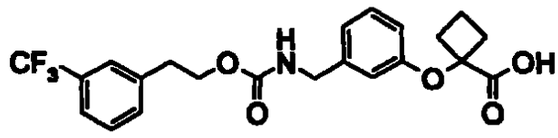
2-(5-Methyl-2-phenyl-2*H*-1,2,3-triazol-4-yl)ethanol (51 mg, 0.25 mmol), methyl 2-[(3'-hydroxybiphenyl-3-yl)oxy]-2-methylpropanoate (86 mg, 0.30 mmol), and Ph_3P (98 mg, 0.375 mmol) were dissolved in anhydrous THF (1 mL) and followed by the dropwise addition of diethyl azodicarboxylate (65 mg, 0.375 mmol) in anhydrous THF (1 mL) at room temperature via a syringe. The resulting reaction solution was stirred at room temperature for 18 hours and concentrated. Purification by silica gel column with 20 - 40% EtOAc in hexane afforded 69 mg (59%) of light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) 1.55 (s, 6 H), 2.31 (s, 3 H), 3.10 (t, 2 H), 3.68 (s, 3 H), 4.25 (t, 2 H), 6.70 (m, 1 H), 6.82 (m, 1 H), 7.00 (s, 1 H), 7.05 (d, 1 H), 7.20 (m, 4 H), 7.32 (t, 2 H), 7.90 (d, 2 H)

LRMS (*m/z*): 472 $(M+H)^+$.

Example B-1

1-(3-[[(2-[3-(Trifluoromethyl)phenyl]ethoxy)carbonyl)amino]methyl]phenoxy)cyclobutane carboxylic acid



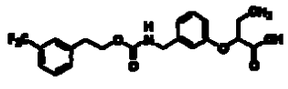
To a solution of ethyl 1-(3-[[(2-[3-(trifluoromethyl)phenyl]ethoxy)carbonyl)amino] methyl]phenoxy)cyclobutanecarboxylate (0.150 g, 0.32 mmol) in tetrahydrofuran (3 mL) and methanol (0.6 mL) at 0 °C was added 2M aqueous lithium hydroxide (0.32 mL, 2 equiv). The resulting mixture was stirred at ambient temperature for 24 hours. Water (10 mL) was added and the mixture was extracted with diethyl ether (1x15 mL, discarded). The aqueous phase was adjusted to pH 2 with 1N hydrochloric acid and extracted with ethyl acetate (3x20 mL). The combined organics were washed with saturated aqueous sodium chloride, dried (anhydrous sodium sulfate), filtered and concentrated to dryness to produce the title compound (85%).

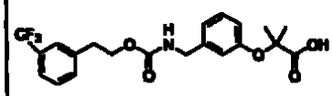
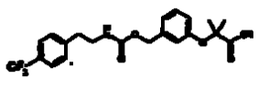
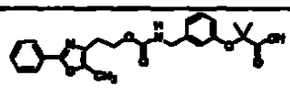
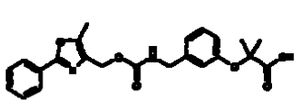
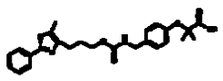
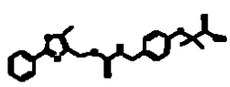
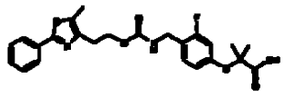
LRMS: 438 $(M+H)^+$.

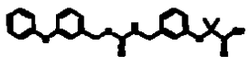
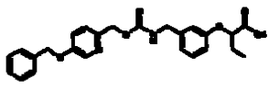
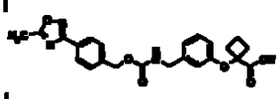
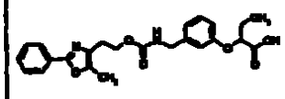
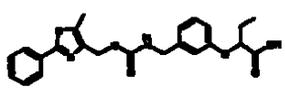
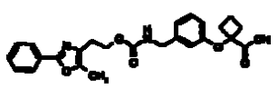
^{1}H NMR ($CDCl_3$, 400 MHz): 7.62 (1H, d, J = 7.8 Hz), 7.46 (1H, t, J = 7.3 Hz), 7.36 (1H, d, J = 7.3 Hz), 7.31 (1H, dd, J = 8.1, 7.6 Hz), 7.18 (1H, t, J = 8.0 Hz), 6.84 (1H, d, J = 7.6 Hz), 6.65 (1H, s), 6.56 (1H, d, J = 7.8 Hz), 4.32-4.27 (4H, m), 3.11 (2H, t, J = 6.8 Hz), 2.79-2.72 (2H, m), 2.49-2.41 (2H, m), 2.09-1.93 (2H, m).

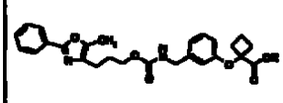
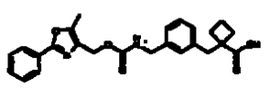
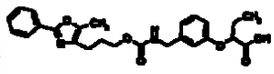
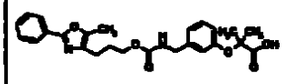
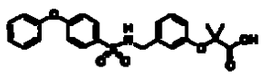
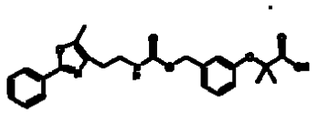
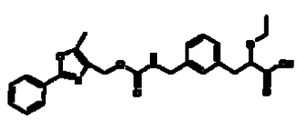
Examples B-2 to B-29

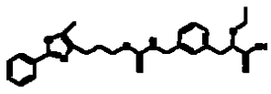
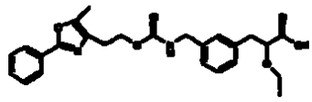
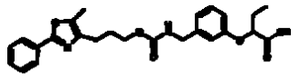
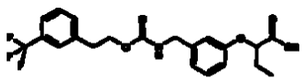
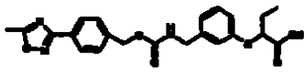
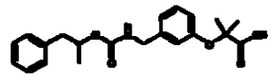
Examples B-2 to B-29 were prepared by procedures analogous to that used for Example B-1.

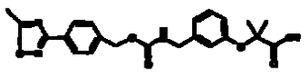
Example #	Structure	^{1}H NMR	MS (m/z) (LR or HR)
B-2		($CDCl_3$, 400 MHz) 7.62 (1H, d, J = 7.8 Hz), 7.46 (1H, t, J = 7.3 Hz), 7.36 (1H, d, J = 7.6 Hz), 7.31 (1H, t, J = 7.6 Hz), 7.22 (1H, t, J = 7.8 Hz), 6.88 (1H, d, J = 7.3 Hz), 6.83 (1H, s), 6.78 (1H, dd, J = 1.9, 8.2 Hz), 4.80 (1H, t, J = 5.8 Hz), 4.36-4.29 (4H, m), 3.11 (2H, t, J = 6.8 Hz), 2.03-1.97 (2H, m), 1.08 (3H, t, J = 7.5 Hz).	For LR 426 $(M+H)^+$

B-3		($CDCl_3$, 400 MHz) 7.62 (1H, d, J = 7.8 Hz), 7.46 (1H, t, J = 7.5 Hz), 7.36 (1H, d, J = 7.6 Hz), 7.31 (1H, t, J = 7.6 Hz), 7.21 (1H, t, J = 7.6 Hz), 6.94 (1H, d, J = 7.3 Hz), 6.86 (1H, s), 6.81 (1H, d, J = 7.8 Hz), 4.36-4.29 (4H, m), 3.11 (2H, t, J = 7.0 Hz), 1.58 (6H, s).	for LR 426 $(M+H)^+$
B-4		^{1}H NMR (400 MHz, $CDCl_3$) : 1.69 (s, 6 H), 4.34 (d, 2 H), 5.05 – 5.17 (m, 1 H), 5.23 (s, 2 H), 6.71 (dd, 1 H), 6.78 (s, 1 H), 6.90 (d, 1 H), 7.18 – 7.23 (m, 1 H), 7.26 – 7.33 (m, 1 H), 7.69 (d, 1 H), 7.89 (d, 1 H), 8.73 (s, 1 H).	LRMS (*m/z*): 426.4 $(M+H)^+$.
B-5		($CDCl_3$, 400 MHz) 7.98-7.92 (2H, m), 7.44-7.38 (3H, m), 7.15 (1H, t, J = 7.7 Hz), 6.87 (1H, s), 6.84-6.79 (2H, m), 4.33-4.28 (4H, m), 2.89 (2H, t, J = 6.8 Hz), 2.32 (3H, s), 1.60 (6H, s).	for LR 439 $(M+H)^+$
B-6		^{1}H NMR (400 MHz, $CDCl_3$) : 1.58 (d, 6 H), 2.46 (s, 3 H), 4.32 (d, 2 H), 5.06 (s, 2 H), 6.70-6.72(m, 1H), 6.89-6.91(m, 1H), 7.23 – 7.28 (m, 2 H), 7.39 – 7.48 (m, 2 H), 7.96 – 8.05 (m, 2 H).	LRMS (*m/z*): 423.5 $(M+H)^+$
B-7		^{1}H NMR (400 MHz, $CDCl_3$) : 1.63 (m, 6 H), 1.95-2.01(m, 2H), 2.34 (s, 3 H), 2.56-2.58 (m, 2 H), 4.11-4.13(m, 2H), 4.32-4.35(d, 2H), 4.89-4.92(b, 1H), 6.82-6.83(m, 2H), 7.21 – 7.27 (m, 3 H) 7.36 – 7.44 (m, 2 H), 7.93-7.96(m, 2H).	LRMS (*m/z*): 453.5 $(M+H)^+$.
B-8		^{1}H NMR (400 MHz, $CDCl_3$) : 1.59 (s, 6 H), 2.47 (s, 3 H), 4.24 – 4.32 (m, 2 H), 4.99 – 5.09 (m, 3 H), 6.73 – 6.80 (m, 2 H), 7.15 (d, 2 H), 7.21 – 7.27 (m, 1 H), 7.37 – 7.46 (m, 2 H), 7.96 – 8.04 (m, 2 H).	LRMS (*m/z*): 425.5 $(M+H)^+$
B-9		^{1}H NMR (400 MHz, $CDCl_3$) : 1.64 (m, 6 H), 2.35 (s, 3 H), 2.82 (t, 2 H), 4.28 – 4.38 (m, 4 H), 6.55 (d, 2 H), 7.17 – 7.28 (m, 2 H), 7.36 – 7.45 (m, 2 H), 7.92 – 8.00 (m, 2 H)	LRMS (*m/z*): 457.5 $(M+H)^+$.

B-10		^{1}H NMR (400 MHz, $CDCl_3$) : 1.67 (s, 6 H), 4.33 (d, 2 H), 5.03 – 5.14 (m, 3 H), 6.69 (dd, 1 H), 6.78 (s, 1 H), 6.92 (dd, 2 H), 7.01 (d, 3 H), 7.06 – 7.14 (m, 2 H), 7.18 (t, 1 H), 7.25 – 7.36 (m, 3 H).	LRMS (*m/z*): 435.5 $(M+H)^+$.
B-11		^{1}H NMR (400 MHz, $CDCl_3$) : 1.05 – 1.16 (m, 3 H), 2.02-2.04(m, 2H), 4.11 – 4.13 (m, 1 H), 4.48 – 4.58 (m, 2 H), 4.95-5.96(m, 1H), 5.11 (s, 2 H), 5.21(s, 2H), 6.75 (d, 1 H), 6.83 – 6.93 (m, 2 H), 7.10 – 7.21 (m, 1 H), 7.30 – 7.41 (m, 6 H), 8.44 (s, 2 H).	LRMS (*m/z*): 451 $(M+H)^+$
B-12		($CDCl_3$, 400 MHz) 8.06-8.00 (1H, m), 8.01 (1H, d, *J* = 7.6 Hz), 7.47-7.42 (1H, m), 7.43 (1H, d, *J* = 7.8 Hz), 7.19 (1H, t, *J* = 7.8 Hz), 6.87 (1H, d, *J* = 7.1 Hz), 6.66 (1H, s), 6.57 (1H, dd, *J* = 2.3, 8.1 Hz), 5.17 (2H, s), 4.32 (2H, d, *J* = 6.1 Hz), 2.80-2.75 (2H, m), 2.65 (3H, s), 2.49-2.41 (2H, m), 2.03-1.97 (2H, m).	for LR 426 $(M+H)^+$
B-13		^{1}H NMR (400 MHz, $CDCl_3$) 0.85 – 0.95 (m, 3 H), 1.82 (s, 2 H), 2.13 (s, 3 H), 2.62 – 2.73 (m, 2 H), 3.85 (d, 1 H), 3.91 (s, 1 H), 4.30 – 4.41 (m, 2 H), 4.99 (s, 1 H), 6.58 (d, 1 H), 6.66 (s, 2 H), 6.94 – 7.06 (m, 2 H), 7.22 (s, 3 H), 7.70 – 7.81 (m, 2 H).	LRMS (*m/z*): 439 $(M+H)^+$.
B-14		^{1}H NMR (400 MHz, $CDCl_3$) : 1.93 – 2.01 (m, 2 H), 2.46 (s, 3 H), 4.34 (d, 2 H), 4.56-4.57(m, 1H), 5.06 (s, 3 H), 6.74-6.76(m, 1H), 6.82-6.84(m, 1H), 6.89-6.91(m, 1H), 7.19 – 7.28 (m, 2 H), 7.41 – 7.46 (m, 2 H), 7.98 – 8.04 (m, 2 H)	LRMS (*m/z*): 425.5 $(M+H)^+$
B-15			for LR 451 $(M+H)^+$

B-16		($CDCl_3$, 400 MHz) 7.96-7.94 (2H, m), 7.42-7.40 (3H, m), 7.19 (1H, t, J = 7.7 Hz), 6.79 (2H, d, J = 7.6 Hz), 6.60 (1H, s), 4.32 (1H, d, J = 6.1 Hz), 4.20 (2H, s), 2.81-2.75 (2H, m), 2.62-2.59 (1H, m), 2.49-2.41 (3H, m), 2.32-2.28 (2H, m), 2.08 (3H, s), 2.00-1.92 (3H, m).	for LR 465 $(M+H)^+$
B-17		^{1}H NMR (400 MHz, $CDCl_3$) : 1.94 – 2.05 (m, 2 H), 2.38 – 2.48 (m, 5 H), 2.68 – 2.76 (m, 2 H), 4.31 (d, 2 H), 5.06 (s, 3 H), 6.52-6.53(m, 1H), 6.65-6.67(m, 1H), 6.83-6.85(m, 1H), 7.16-7.17(m, 1H), 7.41 – 7.46 (m, 3 H) ,7.99 – 8.03 (m, 2 H).	LRMS (*m/z*): 411.4 $(M+H)^+$
B-18			for LR 453 $(M+H)^+$
B-19			for LR 453 $(M+H)^+$
B-20		^{1}H NMR (400 MHz, $CDCl_3$) 1.51 (s, 6 H), 4.02 (d, 2 H), 5.12 (s, 1 H), 6.72 – 6.80 (m, 2 H), 6.89 – 6.96 (m, 2 H), 6.96 – 7.02 (m, 2 H), 7.09 (t, 1 H), 7.29 (s, 2 H), 7.31 – 7.39 (m, 2 H), 7.64 – 7.73 (m, 2 H).	LRMS (*m/z*): 442 $(M+H)^+$.
B-21		^{1}H NMR (400 MHz, $CDCl_3$) : 1.62 (s, 6 H), 2.30 (s, 3 H), 2.69-2.71(m, 2H), 3.49 – 3.68 (m, 2 H), 5.05 (s, 2 H), 5.36-5.38(m, 1H), 6.73-6.75(m, 1H), 6.97-6.99(m, 1H), 7.19 – 7.28 (m, 3 H), 7.38 – 7.48 (m, 1 H), 7.96-7.98 (m, 2H)	LRMS (*m/z*): 439.5$(M+H)^+$.
B-22		^{1}H NMR (400 MHz, $CDCl_3$) : 1.19 – 1.26 (m, 3 H), 2.46 (s, 3 H), 2.93 – 3.02 (m, 2 H), 3.26-3.29 (m, 2H), 3.99-4.01(m, 1H), 4.36 (d, 2 H), 5.06 (s, 3 H), 7.15 (m, 3 H), 7.40 – 7.47 (m, 3 H), 7.98 –	LRMS (*m/z*): 439.5 $(M+H)^+$.

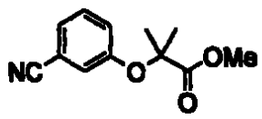
		8.04 (m, 2 H).	
B-23		^{1}H NMR (400 MHz, $CDCl_3$) : 1.21 – 1.27 (m, 3 H), 1.97 – 2.06 (m, 2 H), 2.34 (s, 3 H), 2.57 (t, 2 H), 2.95 – 3.03 (m, 2 H), 3.34-3.59(m, 2H), 4.11 – 4.20 (m, 4 H), 4.35 (d, 2 H), 4.96-4.99(m, 1H), 7.11 – 7.18 (m, 3 H), 7.21 – 7.27 (m, 3 H), 7.37 – 7.45 (m, 2 H), 7.93 – 7.99 (m, 2 H).	LRMS (*m/z*): 467.5 $(M+H)^+$
B-24		^{1}H NMR (400 MHz, $CDCl_3$) : 1.26 – 1.28 (m, 3 H), 2.35 (s, 3 H), 2.86-2.88(m, 2H), 2.95 – 3.06 (m, 1 H), 3.47-3.52(m, 2H), 4.18 – 4.20 (m, 2 H), 4.29 – 4.40 (m, 4 H), 4.96-4.99(m, 1H), 7.10 – 7.18 (m, 2 H), 7.19 – 7.28 (m, 3 H), 7.35 – 7.46 (m, 2 H), 7.92 – 7.99 (m, 2 H).	LRMS (*m/z*): 453.5 $(M+H)^+$.
B-25		^{1}H NMR (400 MHz, $CDCl_3$) : 1.07 (t, 3 H), 1.94 – 2.05 (m, 3 H), 2.17 (s, 3 H), 2.57 (t, 2 H), 4.15 (t, 1 H), 4.17(d, 2H), 4.33 (d, 2 H), 4.58(m, 1H), 6.83(m, 1H), 6.89(m, 1H), 6.95(m, 1H), 7.21 – 7.27 (m, 3 H), 7.37 – 7.44 (m, 2 H), 7.94 – 7.99 (m, 1 H).	LRMS (*m/z*): 453.5 $(M+H)^+$
B-26		^{1}H NMR (400 MHz, $CDCl_3$) : 1.65 (s, 6 H), 2.88 (d, 2 H), 3.46 (s, 2 H), 5.03 (d, 3 H), 6.73 (s, 1 H), 6.83 (d, 1 H), 6.89 – 7.00 (m, 1 H), 7.19 – 7.31 (m, 3 H), 7.55 (t, 2 H)	LRMS (*m/z*): 426.4 $(M+H)^+$.
B-27		$CDCl_3$) : 1.07 (t, 3H), 1.98 (dq, 2 3 (s, 2 H), 4.57-4.59(m, 1H), (s, 2 H), 6.83(m, 1H), 6.89(m, (t, 1 H), 7.48 (d, 2 H), 8.08 (d, 2 H).	LRMS (*m/z*): 426.5 $(M+H)^+$.
B-28		^{1}H NMR (400 MHz, $CDCl_3$) : 1.21 (m, 3 H), 1.57 (s, 6 H), 2.83-2.84 (m, 2H), 4.22 (d, 2 H), 4.83-4.85(b, 1H), 5.23-5.25(m, 1H), 6.84-6.87(m, 3H), 7.13 (dt, 2 H) 7.18 7.23 (m, 4 H).	LRMS (*m/z*): 372.4 $(M+H)^+$.

B-29		^{1}H NMR (400 MHz, $CDCl_3$) : 1.78 (s, 6 H), 2.66 (s, 3H), 4.34 (d, 2 H), 4.85-4.87(b, 1H), 5.05-5.06(s, 2H), 6.53-6.54(m, 1H), 6.67-6.69(m, 1H), 6.83-6.85(m, 1H), 7.13 (dt, 1 H) 7.18 – 7.23 (m, 2 H), 7.95-7.97(m, 2H).	LRMS (*m/z*): 426.5 $(M+H)^+$.

Preparations of starting materials for Examples B-1 to B-29 (Preparations b-1 to b-20)

Preparation b-1

Methyl 2-(3-cyanophenoxy)-2-methylpropanoate



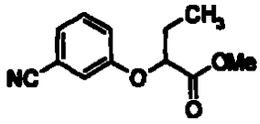
To a solution of 3-cyanophenol (5 mmol) in acetonitrile (20 mL) or any polar, aprotic solvent such as dimethyl sulfoxide, *N,N*-dimethylformamide, etc) was added methyl 2-bromo-2-methyl-propanoate (1.2 equiv) and cesium carbonate (2 equiv). The resulting was mixture heated at 60 °C for 6 hours and then cooled to ambient temperature. Water (20 mL) was introduced and the mixture extracted with ethyl acetate (3x20 mL). The combined organics were washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride, dried (anhydrous sodium sulfate), filtered, and evaporated to dryness to provide the title compound in 75% yield.

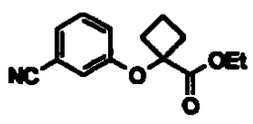
LRMS: 220 $(M+H)^+$.

^{1}H NMR ($CDCl_3$, 400 MHz): 7.30 (1H, t, J = 8.0 Hz), 7.23 (1H, dt, J = 1.3, 7.6 Hz), 7.05 (1H, dd, J = 1.3, 2.3 Hz), 7.01 (1H, ddd, J = 2.3, 2.8, 8.3 Hz), 3.73 (3H, s), 1.57 (6H, s).

Preparations b-2 to b-3

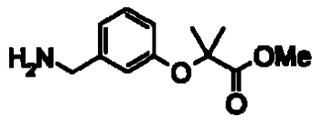
Preparations b-2 to b-3 were prepared using procedures analogous to those described for preparation b-1

Preparation #	Structure	^{1}H NMR	MS (*m/z*) (LR or HR)
2		($CDCl_3$, 400 MHz) 7.33 (1H, dd, J = 7.6, 8.8 Hz), 7.22 (1H, dt, J = 1.3, 7.6 Hz), 7.09-7.08 (2H, m), 4.56 (1H, dd, J = 5.6, 6.6 Hz), 3.73 (3H, s), 2.01-1.93 (2H, m), 1.03 (3H, t, J = 7.5 Hz).	For LR 220 $(M+H)^+$

3		($CDCl_3$, 400 MHz) 7.31 (1H, dd, J = 7.6, 9.1 Hz), 7.22 (1H, dt, J = 1.0, 7.8 Hz), 6.91-6.88 (2H, m), 4.20 (2H, q, J = 7.2 Hz), 2.78-2.71 (2H, m), 2.48-2.40 (2H, m), 2.08-1.98 (2H, m), 1.18 (3H, t, J = 7.2 Hz).	For LR 248 $(M+H)^+$

Preparation b-4

Methyl 2-[3-(aminomethyl)phenoxy]-2-methylpropanoate

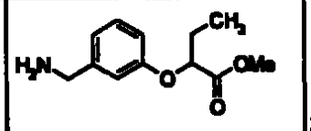
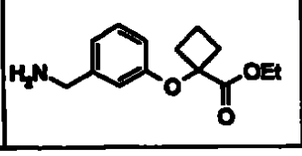


To a solution of methyl 2-(3-cyanophenoxy)-2-methylpropanoate (Preparation b-1) (4 mmol) in methanol (20 mL) was added 10% palladium on carbon (20% by weight). The resulting mixture was stirred under an atmosphere of hydrogen for 24 hours and filtered through Celite. The filtrate was concentrated and the residue taken up in ethyl acetate and washed with 1N hydrochloric acid (2x20 mL). The combined aqueous washes were adjusted to pH >10 with 4N aqueous sodium hydroxide and extracted with dichloromethane (3x20 mL). The combined organic extracts were washed with saturated aqueous sodium chloride, dried (potassium carbonate), filtered and concentrated to dryness to provide the title compound in 65% yield.

LRMS: 224 $(M+H)^+$.

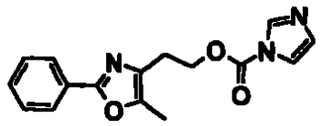
Preparations b-5 to b-6

Preparations b-5 to b-6 were prepared using procedures analogous to those described for preparation b-4

Preparation #	Structure	^1H NMR	MS (*m/z*) (LR or HR)
b-5		($CDCl_3$, 400 MHz) 7.22 (1H, t, J = 7.8 Hz), 6.91 (1H, d, J = 7.6 Hz), 6.86 (1H, s), 6.72 (1H, dd, J = 2.5, 8.1 Hz), 4.58 (1H, t, J = 6.2 Hz), 3.82 (2H, s), 3.74 (3H, s), 2.01-1.94 (2H, m), 1.06 (3H, t, J = 7.6 Hz).	For LR 224 $(M+H)^+$
b-6			for LR 250 $(M+H)^+$

Preparation b-7

2-(5-Methyl-2-phenyl-1,3-oxazol-4-yl)ethyl 1*H*-imidazole-1-carboxylate



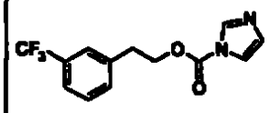
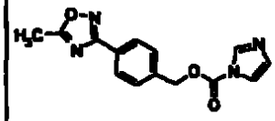
To a solution of 2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)-ethanol (1.015 g, 5 mmol) in toluene (25 mL) was added potassium carbonate (1.38 g, 2 equiv) and *N,N'*-carbonyldiimidazole (0.97 g, 1.2 equiv). The resulting mixture was stirred at ambient temperature for 24 hours before water (20 mL) was introduced. Extraction with ethyl acetate and washing the combined organic extracts with saturated aqueous sodium chloride, drying (anhydrous sodium sulfate), filtration, and concentration to dryness afforded the title compound (100%).

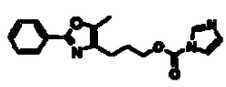
LRMS: 298 $(M+H)^+$.

^{1}H NMR ($CDCl_3$, 400 MHz): 8.10 (1H, s), 7.97-7.93 (2H, m), 7.44-7.39 (5H, m), 4.68 (2H, t, *J* = 6.7 Hz), 2.98 (2H, t, *J* = 6.7 Hz), 2.34 (3H, s).

Preparations b-8 to b-10

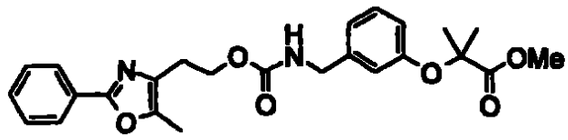
Preparations b-8 to b-10 were prepared using procedures analogous to those described for preparation b-7

Prep #	Structure	^{1}H NMR	MS (*m/z*) (LR or HR)
b-8		($CDCl_3$, 400 MHz) 8.10 (1H, s), 7.68 (1H, d, *J* = 7.6 Hz), 7.52 (1H, t, *J* = 7.6 Hz), 7.40 (1H, s), 7.38 (1H, s), 7.24 (1H, t, *J* = 7.3 Hz), 7.17-7.13 (1H, m), 4.63 (2H, t, *J* = 6.8 Hz), 3.29 (2H, t, *J* = 6.8 Hz).	For LR 285 $(M+H)^+$
b-9		($CDCl_3$, 400 MHz) 8.49 (1H, bs), 8.13 (2H, d, *J* = 8.3 Hz), 7.57 (1H, s), 7.54 (2H, s), 7.28-7.24 (1H, m), 5.52 (2H, s), 2.66 (3H, s).	for LR 285 $(M+H)^+$
b-10			for LR 312 $(M+H)^+$

Preparation b-11

Methyl 2-methyl-2-[3-[[(2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy)carbonyl]amino]methyl] phenoxy]propanoate



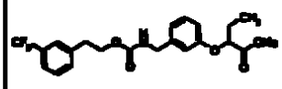
To a solution of 2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethyl 1*H*-imidazole-1-carboxylate (Preparation 7) (0.48 g, 1.6 mmol) in tetrahydrofuran (3 mL) was added methyl 2-[3-(aminomethyl)phenoxy]-2-methylpropanoate (Preparation b-4) (0.39 g, 1.1 equiv). The resulting mixture was heated at reflux for 16 hours and then cooled to ambient temperature. Concentration and purification by silica gel chromatography using 0-50% ethyl acetate in hexanes gave the title compound (0.39 g, 53%).

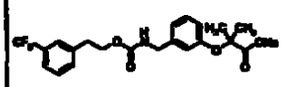
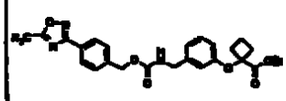
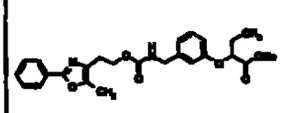
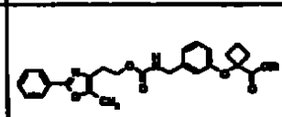
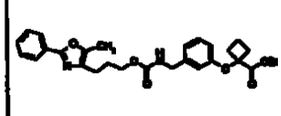
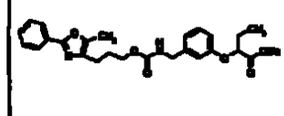
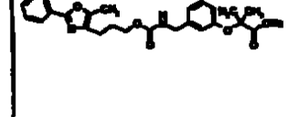
LRMS: 453 $(M+H)^+$.

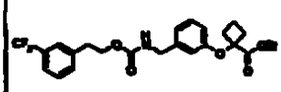
^{1}H NMR ($CDCl_3$, 400 MHz): 7.96 (2H, dd, J = 1.9, 7.7 Hz), 7.44-7.38 (3H, m), 7.16 (1H, t, J = 8.0 Hz), 6.89 (1H, d, J = 7.3 Hz), 6.77 (1H, s), 6.67 (1H, dd, J = 2.3, 8.3 Hz), 4.36 (2H, t, J = 6.7 Hz), 4.30 (2H, d, J = 5.8 Hz), 3.75 (3H, s), 2.83 (2H, t, J = 6.7 Hz), 2.32 (3H, s), 1.57 (6H, s).

Preparations b-12 to b-20

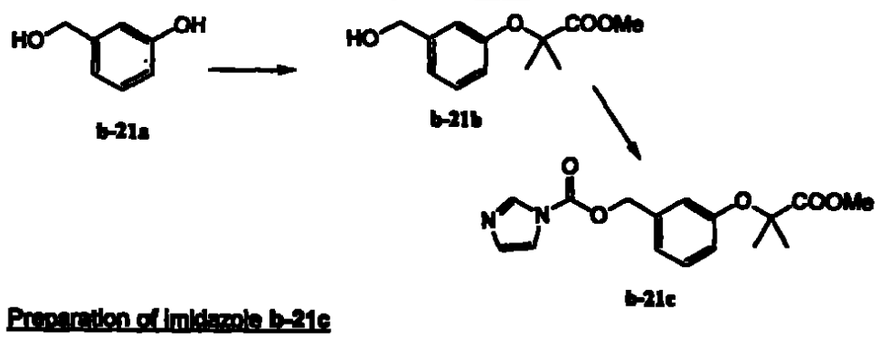
Preparations b-12 to b-20 were prepared using procedures analogous to those used for Preparation b-11

Preparation #	Structure	^{1}H NMR	MS (*m/z*) (LR or HR)
b-12			for LR 440 $(M+H)^+$

b-13		($CDCl_3$, 400 MHz) 7.63 (1H, d, J = 7.8 Hz), 7.47 (1H, t, J = 7.5 Hz), 7.38 (1H, d, J = 8.3 Hz), 7.34-7.28 (1H, m), 7.18 (1H, dd, J = 7.8, 8.1 Hz), 6.89 (1H, d, J = 7.3 Hz), 6.77 (1H, s), 6.69 (1H, dd, J = 2.3, 8.3 Hz), 4.33-4.30 (4H, m), 3.75 (3H, s), 3.13 (2H, t, J = 7.0 Hz), 1.58 (6H, s).	for LR 440 $(M+H)^+$
b-14		($CDCl_3$, 400 MHz) 7.99 (2H, d, J = 8.1 Hz), 7.41 (2H, m), 7.11 (1H, t, J = 8.1 Hz), 6.79 (1H, d, J = 7.6 Hz), 6.60 (1H, s), 6.46 (1H, dd, J = 2.3, 8.1 Hz), 5.12 (2H, s), 4.27 (2H, d, J = 6.1 Hz), 4.12 (2H, q, J = 7.1 Hz), 2.71-2.60 (2H, m), 2.59 (3H, s), 2.42-2.32 (2H, m), 1.98-1.88 (2H, m), 1.09 (3H, t, J = 7.1 Hz).	For LR 440 $(M+H)^+$
b-15			for LR 453 $(M+H)^+$
b-16		($CDCl_3$, 400 MHz) 7.96 (2H, dd, J = 1.9, 7.7 Hz), 7.44-7.36 (3H, m), 7.18-7.13 (1H, m), 6.85 (1H, d, J = 7.6 Hz), 6.66 (1H, s), 6.50 (1H, dt, J = 1.3, 8.1 Hz), 4.35 (2H, t, J = 7.1 Hz), 4.29 (2H, d, J = 6.1 Hz), 4.11 (2H, q, J = 7.1 Hz), 2.83 (2H, t, J = 6.8 Hz), 2.77-2.69 (2H, m), 2.48-2..38 (2H, m), 2.32 (3H, s), 2.01-1.94 (2H, m), 1.16 (3H, t, J = 7.2 Hz).	For LR 479 $(M+H)^+$
b-17		($CDCl_3$, 400 MHz) 7.96 (2H, dd, J = 1.8, 7.8 Hz), 7.43-7.38 (3H, m), 7.17 (1H, t, J = 7.8 Hz), 6.85 (1H, d, J = 7.8 Hz), 6.66 (1H, s), 6.50 (1H, dd, J = 2.3, 8.1 Hz), 4.30 (2H, d, J = 5.8 Hz), 4.19 (2H, q, J = 7.3 Hz), 4.18-4.08 (2H, t, J = 7.5 Hz), 2.77-2.69 (2H, m), 2.56 (2H, t, J = 7.5 Hz), 2.48-2.39 (2H, m), 2.30 (3H, s), 2.02-1.94 (4H, m), 1.16 (3H, t, J = 7.1 Hz).	For LR 493 $(M+H)^+$
b-18		($CDCl_3$, 400 MHz) 7.96 (2H, dd, J = 1.8, 7.8 Hz), 7.43-7.38 (3H, m), 7.22 (1H, t, J = 8.1 Hz), 6.89 (1H, d, J = 7.8 Hz), 6.82 (1H, s), 6.74 (1H, dd, J = 2.2, 8.2 Hz), 4.56 (1H, t, J = 6.2 Hz), 4.32 (2H, d, J = 5.8 Hz), 4.14 (2H, t, J = 6.3 Hz), 3.74 (3H, s), 2.56 (2H, t, J = 7.3 Hz), 2.30 (3H, s), 2.03-1.93 (4H, m), 1.06 (3H, t, J = 7.3 Hz).	For LR 467 $(M+H)^+$
b-19		($CDCl_3$, 400 MHz) 7.96 (2H, dd, J = 1.8, 7.8 Hz), 7.43-7.38 (3H, m), 7.18 (1H, t, J = 8.0 Hz), 6.90 (1H, d, J = 7.6 Hz), 6.78 (1H, s), 6.68 (1H, dd, J = 2.2, 8.0 Hz), 4.31 (2H, d, J = 6.1 Hz), 4.13 (2H, t, J = 6.1 Hz), 3.75 (3H, s), 2.56 (2H, t, J = 7.3 Hz), 2.30 (3H, s), 2.00 (2H, t, J = 7.1 Hz), 1.58 (6H, s).	for LR 467 $(M+H)^+$

b-20		($CDCl_3$, 400 MHz) 7.63 (1H, d, J = 7.8 Hz), 7.47 (1H, t, J = 7.6 Hz), 7.38 (1H, d, J = 7.6 Hz), 7.32 (1H, t, J = 7.7 Hz), 7.16 (1H, t, J = 8.0 Hz), 6.83 (1H, d, J = 7.3 Hz), 6.65 (1H, s), 6.51 (1H, dd, J = 2.3, 8.1 Hz), 4.33-4.29 (4H, m), 4.18 (2H, q, J = 7.1 Hz), 3.13 (2H, t, J = 7.0 Hz), 2.76-2.69 (2H, m), 2.47-2.39 (2H, m), 2.01-1.94 (2H, m), 1.16 (3H, t, J = 7.1 Hz).	For LR 412 $(M+H)^+$

Preparation b-21

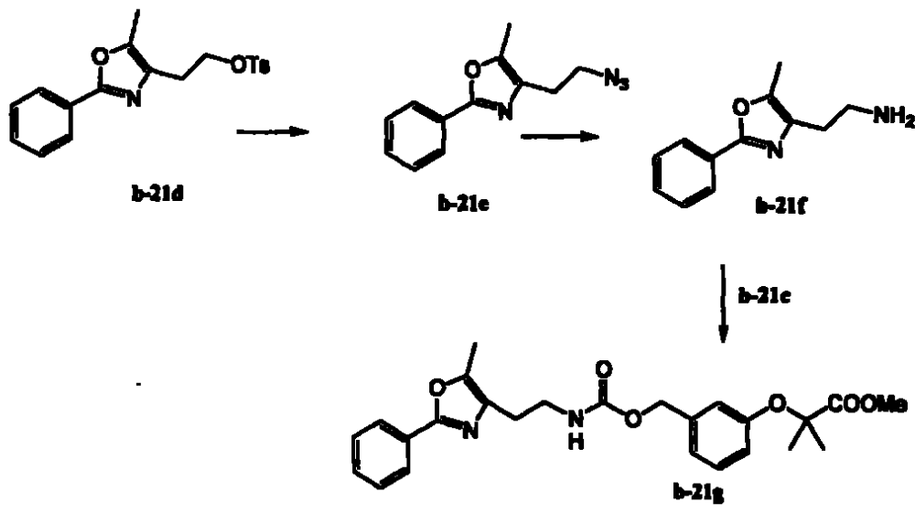


Preparation of imidazole b-21c

To a solution of the alcohol b-21b (1 mmol) in toluene (5 ml) were added N, N'-carbonyldiimidazole (1.05 mmol) and potassium carbonate (1 mmol). The resulting solution heated at reflux for 3 hr. After cooling to room temperature, water (20 ml) was added and the mixture extracted with ethyl acetate (3x20 ml). The combined extracts were washed with brine, dried over sodium sulfate and concentrated in vacuo to provide the acyl imidazole b-21c in quantitative yield.

Preparation of alcohol b-21b

To a solution of 3-hydroxybenzyl alcohol b-21a (1 mmol) and cesium carbonate (1 mmol) in acetonitrile (10 ml) was added methyl 2-bromo-2-methyl propionate (2 mmol). The mixture was heated under reflux for 6 hours. After cooling to room temperature, water (50 ml) was introduced and the mixture extracted with ethyl acetate (3x20 ml). Combined organics were washed with brine, dried over sodium sulfate and evaporated in vacuo. Silica gel chromatography (SGC) using 10-30% ethyl acetate-hexane gave alcohol b-21b. Yields ranged between 40-85%.



Preparation of methyl ester b-21g

Following the procedures described in b-11, methyl ester b-21g was prepared by reacting compound b-21f with compound b-21c in yields ranging from 60 to 90%.

Preparation of amine b-21f

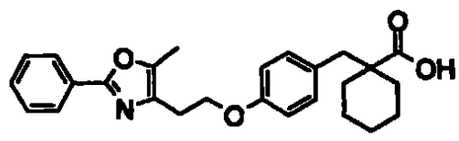
A solution of the azide b-21e (2 mmol) in ethyl acetate (20 ml) and palladium on carbon (10% by weight, 50 mg) was treated with hydrogen gas at room temperature for 4 hours. Removal of palladium by filtration through a pad of Celite and concentration produced the amine b-21f in quantitative yield.

Preparation of azideb-21e

To a solution of the tosylate b-21d (1 mmol) in DMF (5 ml) was added sodium azide (3 mmol). The resulting mixture stirred at room temperature for 14 hours before water (50 ml) was added. Extraction with ethyl acetate (3x20 ml), washing of the combined organics with water, saturated sodium bicarbonate and brine, drying over sodium sulfate and concentration gave rise to the azide b-21e in 85% yield.

Example C-1

1-{4-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]benzyl}cyclohexanecarboxylic acid



Triethylsilane (1.03 g, 8.86 mmol) was added to a solution of methyl 1-(hydroxyl(4-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]phenyl}methyl)cyclohexanecarboxylate (0.797 g, 1.77 mmol) in dichloromethane (5 mL) and trifluoroacetic acid (1 mL) at room temperature. The resulting mixture was stirred for 1 hour then evaporated *in vacuo* and azeotroped with heptane. The residue was dissolved in tetrahydrofuran (3 mL) and water (3 mL) and lithium hydroxide monohydrate (0.223 g, 5.31 mmol) was added. The resulting mixture was stirred at room temperature for 18 hours, acidified to pH 2 with 4N hydrochloric acid and extracted with ethyl acetate. The organic phase was dried (anhydrous magnesium sulfate), filtered and evaporated to afford the title compound (0.332 g, 45%).

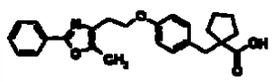
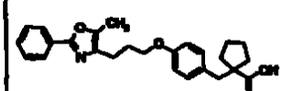
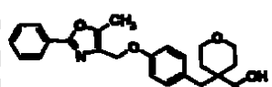
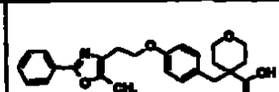
Elemental Analysis: Calcd for $C_{29}H_{29}NO_4$ C 74.44, H 6.97, N 3.34. Found:C 74.22, H 6.89, N 3.34.

LRMS: 420 $(M+H)^+$.

^{1}H NMR (DMSO-d_6, 400 MHz): 7.90 (2H, dd, J = 1.8, 7.8 Hz), 7.51-7.46 (3H, m), 6.98 (2H, d, J = 8.6 Hz), 6.80 (2H, d, J = 8.6 Hz), 4.16 (2H, t, J = 6.6 Hz), 2.90 (2H, t, J = 6.6 Hz), 2.64 (2H, s), 2.34 (3H, s), 1.85 (2H, d, J = 12.6 Hz), 1.53-1.46 (3H, m), 1.29-1.11 (5H, m).

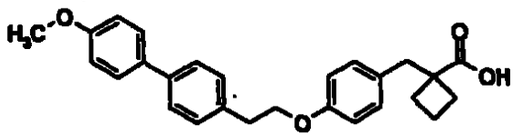
Examples C-2 to C-5

Examples C-2 to C-5 were prepared by procedures analogous to those used for Example C-1 with the exception that the final hydrolysis step was carried out by dissolving the crude residue in dimethyl sulfoxide (75 mg/mL) and 6N sodium hydroxide (1 mL) and heating at 150 °C for 10 minutes in a microwave synthesizer.

Ex #	Structure	^{1}H NMR	MS (*m/z*) (LR or HR)	Analysis
C-2		(DMSO-d_6, 400 MHz) 7.90 (2H, dd, *J* = 1.9, 7.7 Hz), 7.51-7.44 (3H, m), 7.04 (2H, d, *J* = 8.6 Hz), 6.80 (2H, d, *J* = 8.6 Hz), 4.15 (2H, t, *J* = 6.7 Hz), 2.90 (2H, t, *J* = 6.6 Hz), 2.79 (2H, s), 2.34 (3H, s), 2.05-2.00 (2H, m), 1.75-1.60 (6H, m).	for LR 406 (M+H)+	Calcd for $C_{25}H_{27}NO_4$ C 74.05, H 6.71, N 3.45. Found: C 73.83, H 6.69, N 3.36.
C-3		(DMSO-d_6, 400 MHz) 7.89 (2H, dd, *J* = 1.8, 7.8 Hz), 7.51-7.46 (3H, m), 7.04 (2H, d, *J* = 8.6 Hz), 6.81 (2H, d, *J* = 8.6 Hz), 3.93 (2H, t, *J* = 6.2 Hz), 2.79 (2H, s), 2.60 (2H, t, *J* = 7.3 Hz), 2.27 (3H, s), 2.04-1.97 (2H, m), 1.92-1.85 (2H, m), 1.61-1.46 (6H, m).	for LR 420 (M+H)$^+$	Calcd for $C_{26}H_{29}NO_4$ C 74.44, H 6.97, N 3.34. Found: C 74.30, H 6.95, N 3.26.
C-4		(DMSO-d_6, 400 MHz) 7.94-7.92 (2H, m), 7.54-7.48 (3H, m), 7.04 (2H, d, *J* = 8.6 Hz), 6.92 (2H, d, *J* = 8.6 Hz), 4.95 (2H, s), 3.75-3.70 (2H, m), 3.28 (2H, dd, *J* = 10.0, 11.2 Hz), 2.73 (2H, s), 2.43 (3H, s), 1.81 (2H, d, *J* = 13.1 Hz), 1.49-1.42 (2H, m).	for LR 408 (M+H)$^+$	Calcd for $C_{24}H_{25}NO_5$ C 70.75, H 6.18, N 3.44. Found: C 70.60, H 6.33, N 3.31.
C-5		(DMSO-d_6, 400 MHz) 7.90 (2H, dd, *J* = 1.9, 7.7 Hz), 7.51-7.44 (3H, m), 6.99 (2H, d, *J* = 8.6 Hz), 6.81 (2H, d, *J* = 8.6 Hz), 4.16 (2H, t, *J* = 6.6 Hz), 3.74-3.69 (2H, m), 3.27 (2H, t, *J* = 10.6 Hz), 2.90 (2H, t, *J* = 6.4 Hz), 2.71 (2H, s), 2.34 (3H, s), 1.79 (2H, d, *J* = 13.1 Hz), 1.47-1.39 (2H, m).	for LR 422 (M+H)$^+$	Calcd for $C_{25}H_{27}NO_5$ C 71.24, H 6.46, N 3.32. Found: C 71.01, H 6.47, N 3.32.

Example C-6

1-{4-[2-(4'-methoxy-1,1'-biphenyl-4-yl)ethoxy]benzyl}cyclobutanecarboxylic acid



To a solution of ethyl 1-{4-[2-(4'-methoxy-1,1'-biphenyl-4-yl)ethoxy]benzyl} cyclobutanecarboxylate (Preparation 14) (0.3921 mmol, 1 equiv.) in acetonitrile (2 mL) was added 1N aqueous sodium hydroxide (7.2 mL, 8 equiv.). The resulting mixture was subjected to microwave heating (100 °C) in a Personal Chemistry Smith Synthesizer for 40 minutes. Following cooling of the reaction mixture, 1M

aqueous hydrochloric acid was added until pH 1 was achieved. The mixture was extracted with ethyl acetate (3x50 mL). The combined organic extracts were then washed with saturated aqueous sodium chloride (100 mL), dried (anhydrous magnesium sulfate), filtered and concentrated *in vacuo* to afford the crude product. The residue was purified by trituration from diethyl ether to afford the title compound as a white crystalline solid (0.1321 g, 81%).

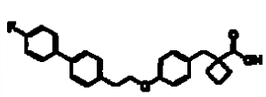
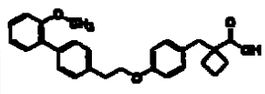
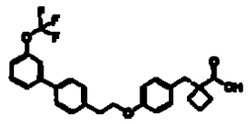
Elemental Analysis: Calcd for $C_{27}H_{28}O_4$ C 77.86, H 6.78. Found:C 77.65, H 6.85.

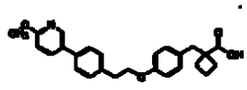
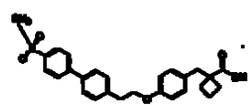
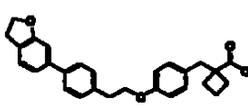
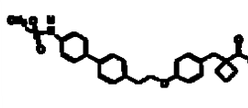
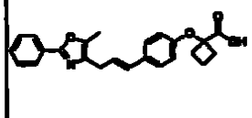
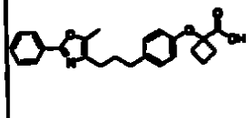
LRMS (*m/z*): 416 $(M)^-$.

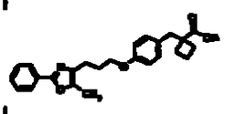
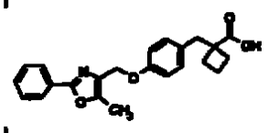
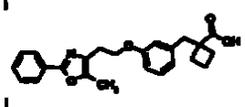
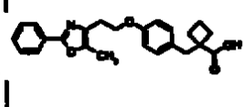
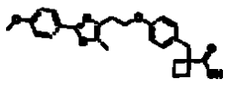
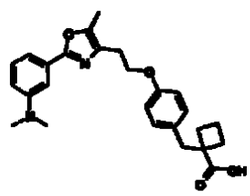
^{1}H NMR (Acetone-d_6, 300 MHz): 7.53 (2H, d, *J* = 6.1 Hz), 7.66 (2H, d, *J* = 5.1 Hz), 7.46 (2H, d, *J* = 8.5 Hz), 7.13 (2H, d, *J* = 8.7 Hz), 7.07 (2H, d, *J* = 8.7 Hz), 6.85 (2H, d, *J* = 8.5 Hz), 4.20 (1H, t, *J* = 6.1 Hz), 3.86 (3H, s), 3.10 (2H, t, *J* = 7.0 Hz), 3.00 (2H, s), 2.40-2.30 (2H, m), 2.07-1.98 (2H, m), 1.92-1.80 (2H, m).

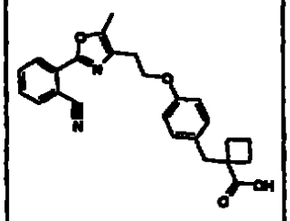
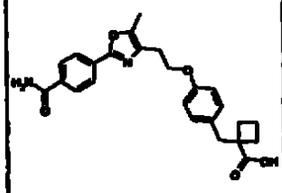
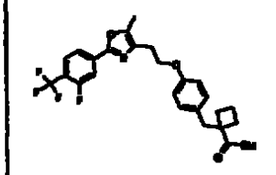
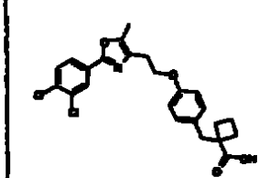
Examples C-7 to C-93

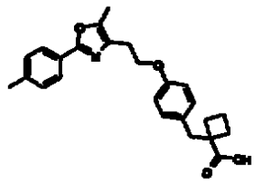
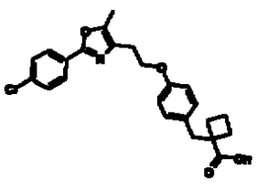
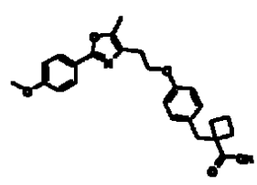
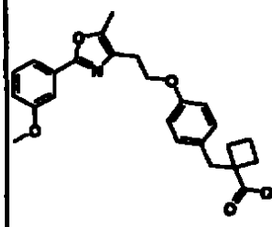
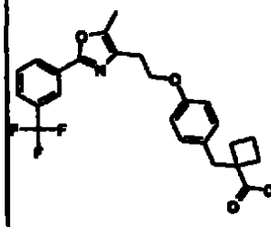
Examples C-7 to C-93 were prepared by procedures analogous to those used for Example C-6 or by stirring a solution of the ester with sodium or lithium hydroxide in aqueous methanol, aqueous ethanol, aqueous tetrahydrofuran or mixtures thereof at temperatures between 20 °C and 75°C.

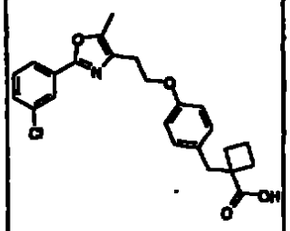
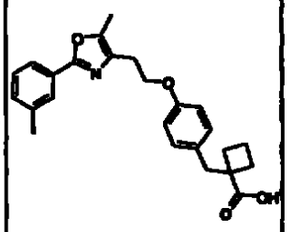
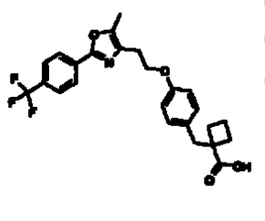
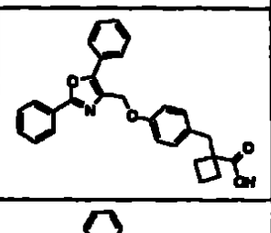
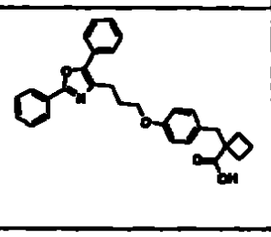
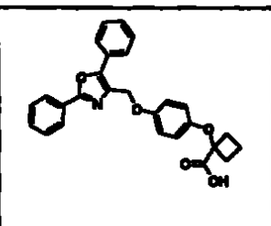
Ex #	Structure	^{1}H NMR	MS (*m/z*) (LR or HR)	Analysis
C-7		(Acetone-d_6, 300 MHz) 7.48 (2H, d, *J* = 8.9 Hz), 7.58 (2H, d, *J* = 8.7 Hz), 7.41 (2H, d, *J* = 8.5 Hz), 7.13 (2H, t, *J* = 8.9 Hz), 7.07 (2H, d, *J* = 8.7 Hz), 6.78 (2H, d, *J* = 8.7 Hz), 4.14 (2H, t, *J* = 7.0 Hz), 3.03 (2H, t, *J* = 7.0 Hz), 2.97 (2H, s), 2.40-2.30 (2H, m), 2.01-1.92 (2H, m), 1.85-1.72 (2H, m).	for LR 404 $(M)^-$	Calcd for $C_{28}H_{25}FO_3$ C 77.21, H 6.23. Found: C 77.13, H 6.28.
C-8		(Acetone-d_6, 300 MHz) 7.58 (2H, d, *J* = 8.3 Hz), 7.41 (2H, d, *J* = 8.3 Hz), 7.34 (1H, t, *J* = 7.9 Hz), 7.21-7.15 (2H, m), 7.12 (2H, d, *J* = 8.7 Hz), 6.90 (1H, ddd, *J* = 0.94, 2.64, 8.3 Hz), 6.83 (2H, d, *J* = 8.7 Hz), 4.19 (2H, t, *J* = 6.9 Hz), 3.85 (3H, s), 3.09 (2H, t, *J* = 6.8 Hz), 3.02 (2H, s), 2.39-2.30 (2H, m), 2.07-1.98 (2H, m), 1.89-1.81 (2H, m)	for LR 416 $(M)^-$	Calcd for $C_{27}H_{28}O_4$ C 77.86, H 6.78. Found: C 77.67, H 6.67.
C-9		(Acetone-d_6, 300 MHz) 7.69 (1H, dt, *J* = 0.9, 8.3 Hz), 7.65 (2H, d, *J* = 8.3 Hz), 7.58 (2H, t, *J* = 8.1 Hz), 7.47 (2H, d, *J* = 8.3 Hz), 7.31 (1H, dt, *J* = 1.1, 8.1 Hz), 7.13 (2H, d, *J* = 8.7 Hz), 6.83 (2H, d, *J* = 8.7 Hz), 4.21 (2H, t, *J* = 6.8 Hz), 3.12 (2H, t, *J* = 6.8 Hz), 3.03 (2H, s), 2.40-2.30 (2H, m), 2.08-1.98 (2H, m), 1.92-1.79 (2H, m)	for LR 470 $(M)^-$	Calcd for $C_{27}H_{25}F_3O_4$ C 68.93, H 5.36. Found: C 69.04, H 5.47.

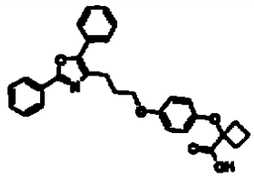
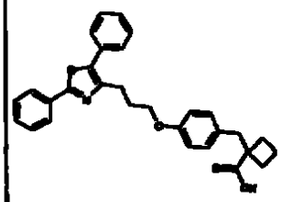
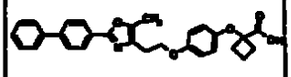
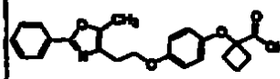
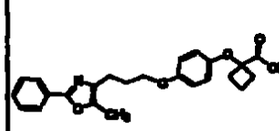
C-10		(Acetone-d_6, 300 MHz) 8.42 (1H, d, J = 2.6 Hz), 7.93 (1H, dd, J = 2.6, 8.7 Hz), 7.57 (2H, d, J = 8.3 Hz), 7.44 (2H, d, J = 8.3 Hz), 7.13 (2H, d, J = 8.9 Hz), 6.84 (2H, d, J = 8.7 Hz), 6.85-6.81 (1H, m), 4.20 (2H, t, J = 6.8 Hz), 3.91 (3H, s), 3.10 (2H, t, J = 7.0 Hz), 3.03 (2H, s), 2.40-2.30 (2H, m), 2.07-1.99 (2H, m), 1.90-1.82 (2H, m).	for LR 417 $(M)^-$	Calcd for $C_{28}H_{27}NO_4$ C 74.80, H 6.52, H 3.35. Found: C 74.67, H 6.46, N 3.31.
C-11		(Acetone-d_6, 300 MHz) 8.01 (2H, d, J = 8.5 Hz), 7.92 (2H, d, J = 8.5 Hz), 7.70 (2H, d, J = 8.5 Hz), 7.50 (2H, d, J = 8.1 Hz), 7.13 (2H, d, J = 8.7 Hz), 6.84 (2H, d, J = 8.7 Hz), 4.22 (2H, t, J = 6.8 Hz), 3.15 (3H, s), 3.13 (2H, t, J = 6.8 Hz), 3.03 (2H, s), 2.40-2.30 (2H, m), 2.07-1.98 (2H, m), 1.92-1.79 (2H, m).	for LR 482 $(M)^-$	Calcd for $C_{27}H_{29}O_6S$ C 69.80, H 6.07. Found: C 69.41, H 6.12.
C-12		(Acetone-d_6, 300 MHz) 7.53-7.48 (1H, m), 7.52 (2H, d, J = 8.3 Hz), 7.38-7.34 (1H, m), 7.37 (2H, d, J = 8.3 Hz), 7.13 (2H, d, J = 8.7 Hz), 6.83 (2H, d, J = 8.7 Hz), 6.78 (1H, d, J = 8.3 Hz), 4.57 (2H, t, J = 8.7 Hz), 4.18 (2H, t, J = 6.8 Hz), 3.25 (2H, t, J = 8.7 Hz), 3.08 (2H, t, J = 7.0 Hz), 3.03 (2H, s), 2.40-2.30 (2H, m), 2.07-1.99 (2H, m), 1.92-1.79 (2H, m).	for LR 428 $(M)^-$	Calcd for $C_{28}H_{29}O_4$ C 78.48, H 6.59. Found: C 78.30, H 6.82.
C-13		(Acetone-d_6, 300 MHz) 7.65 (2H, d, J = 8.7 Hz), 7.59 (2H, d, J = 8.1 Hz), 7.42 (4H, dd, J = 1.5, 8.1 Hz), 7.13 (2H, d, J = 8.5 Hz), 6.84 (2H, d, J = 8.9 Hz), 4.20 (2H, t, J = 6.8 Hz), 3.10 (2H, t, J = 6.8 Hz), 3.03 (2H, s), 3.01 (3H, s), 2.40-2.30 (2H, m), 2.07-1.99 (2H, m), 1.92-1.81 (2H, m).	for LR 479 $(M)^-$	Calcd for $C_{27}H_{29}NO_5S$ C 67.82, H 6.09, N 2.92. Found: C 67.36, H 6.11, N 2.85.
C-14		^{1}H NMR (400 MHz, $CDCl_3$) 2.29 (s, 3 H), 2.39 (m, 2 H), 2.75 (m, 2 H), 3.00 (q, 2 H), 3.30 (d, 2 H), 6.00 (td, 1 H), 6.25 (d, 1 H), 6.56 (d, 2 H), 7.08 (d, 2 H), 7.35 (m, 3 H), 7.90 (m, 2 H).	LRMS (*m/z*): 390 $(M+H)^+$.	
C-15		^{1}H NMR (400 MHz, $CDCl_3$) 1.77 1.89 (m, 2 H), 1.93 2.05 (m, 2 H), 2.27 (s, 3 H), 2.40 2.51 (m, 6 H), 2.71 2.80 (m, 2 H), 6.63 (d, 2 H), 6.97 (d, 2 H), 7.40 (dd, 3 H), 7.92 (m, 2 H).	LRMS (*m/z*): 392 $(M+H)^+$.	

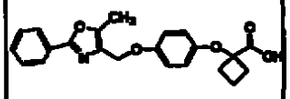
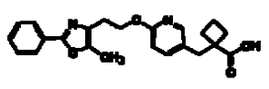
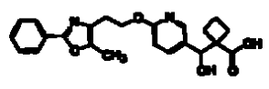
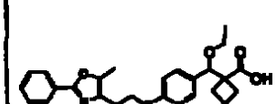
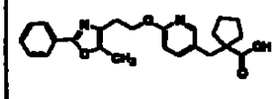
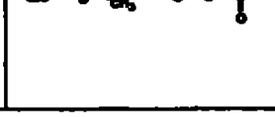
C-16		(DMSO-d_6, 400 MHz) 12.13 (1H, s), 7.86 (2H, m), 7.49-7.40 (3H, m), 7.01 (2H, d, J = 8.8Hz) 6.78 (2H, t, J = 8.6Hz), 3.90 (2H, t, J = 6.3Hz), 2.89 (2H, s), 2.56 (2H, t, J = 7.3Hz), 2.24 (3H, s), 2.24-2.15 (2H, m) 2.00-1.67 (6H, m).	Calcd for $C_{25}H_{28}NO_4$ 406.2013. Found: 406.2002.	Calcd for $C_{25}H_{27}NO_4$ C 74.05, H 6.71, N 3.45. Found: C 73.75, H 6.64, N 3.44.
C-17		(DMSO-d_6, 400 MHz) 12.04 (1H,s), 7.79 (2H, m), 7.40-7.34 (3H, m), 6.95 (2H, d, J = 8.6Hz), 6.78 (2H, t, J = 8.6Hz), 4.80 (2H, s), 2.80 (2H, s), 2.28 (3H, s), 2.12-2.06 (2H, m) 1.83-1.57 (4H, m).	Calcd for $C_{23}H_{24}NO_4$ 378.1700. Found: 378.1692.	Calcd for $C_{23}H_{23}NO_4$ C 73.19, H 6.14, N 3.71. Found: C 73.15, H 6.26, N 3.75.
C-18		($CDCl_3$, 400 MHz) 8.00-7.97 (2H, m), 7.49-7.40 (3H, m), 7.17 (1H, t, J = 7.8Hz), 7.03 (1H, s), 6.78 (2H, t, J = 7.1Hz), 4.24 (2H, t, J = 8.1Hz), 3.14 (2H, s), 2.90 (2H, t, J = 7.8Hz), 2.51-2.40 (2H, m), 2.38 (3H, s), 2.07-1.83 (4H, m).	Calcd for $C_{24}H_{26}NO_4$ 392.1857. Found: 392.1859.	Calcd for $C_{24}H_{25}NO_4 0.2H_2O$ C 72.96, H 6.48, N 3.55. Found: C 72.66, H 6.65, N 3.47.
C-19		(DMSO-d_6, 400 MHz) 7.90 (2H, dd, J = 1.9, 7.7 Hz), 7.51-7.44 (3H, m), 7.05 (2H, d, J = 8.6 Hz), 6.81 (2H, d, J = 8.6 Hz), 4.15 (2H, t, J = 6.7 Hz), 2.92 (2H, s), 2.90 (2H, t, J = 6.8 Hz), 2.34 (3H, s), 2.25-2.18 (2H, m), 1.95-1.88 (2H, m), 1.86-1.71 (2H, m).	for LR 392 $(M+H)^+$	Calcd for $C_{24}H_{25}NO_4$ C 73.64, H 6.44, N 3.58. Found: C 73.49, H 6.46, N 3.54.
C-20		^{1}H NMR (DMSO-d_6, 400 MHz) : 7.83 (2H, d, J = 9.1 Hz), 7.06-7.02 (4H, m), 6.82 (2H, d, J = 8.6 Hz), 4.17 (2H, t, J = 6.3 Hz), 3.80 (3H, s), 3.10 (2H, t, J = 6.3 Hz), 2.92 (2H, s), 2.25-2.17 (2H, m), 2.06 (3H, s), 1.95-1.69 (4H, m).	Calcd for $C_{25}H_{28}NO_5$ 422.1962. Found: 422.1961	
C-21		(DMSO-d6, 400 MHz) 7.25-7.24 (1H, m), 7.19-7.17 (2H, m), 7.00-6.97 (2H, m), 6.76-6.75 (1H, m), 6.72-6.70 (2H, m), 4.10 (2H, t, J = 6.5 Hz), 2.90 (6H, s), 2.85 (2H, t, J = 6.5 Hz), 2.25 (3H, s), 2.24-2.21 (2H, m), 1.95-1.92 (2H, m), 1.78-1.74 (2H, m).	HR Calcd for $C_{25}H_{30}N_2O_4$ $(M+H)^+$ 435.2279. Found	

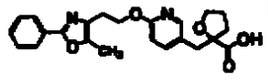
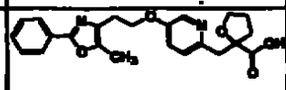
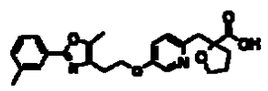
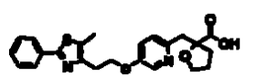
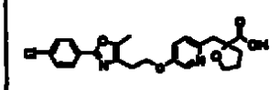
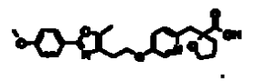
			435.2270. For LR 435 $(M+H)^+$	
C-22		($CDCl_3$, 400 MHz) 8.13-8.11 (1H, m), 7.77-7.75 (1H, m), 7.68-7.62 (1H, m), 7.49-7.45 (1H, m), 7.09-7.07 (2H, m), 6.81-6.79 (2H, m), 4.23 (2H, t, J = 6.3 Hz), 3.03 (2H, s), 2.99 (2H, t, J = 6.3 Hz), 2.48-2.38 (2H, m), 2.40 (3H, s), 2.09-2.02 (2H, m), 1.90-1.86 (2H, m).	HR Calcd for $C_{25}H_{24}N_2O_4$ $(M+H)^+$ 417.1809. Found 417.1813. For LR 418 $(M+H)^+$	
C-23		(DMSO-d6, 400 MHz) 12.04 (1H, s), 7.89-7.84 (4H, m), 6.96-6.94 (2H, m), 6.72-6.70 (2H, m), 4.06 (2H, t, J = 6.5 Hz), 3.06-3.05 (1H, m), 2.82-2.80 (4H, m), 2.26 (3H, s), 2.15-2.08 (2H, m), 1.83-1.79 (2H, m), 1.69-1.65 (2H, m).	HR Calcd for $C_{25}H_{25}N_2O_5$ $(M+H)^+$ 435.1915. Found 435.1922. For LR 435 $(M+H)^+$	
C-24		($CDCl_3$, 300 MHz) 7.84-7.76 (2H, m), 7.66-7.61 (1H, m), 7.09-7.06 (2H, m), 6.80-6.77 (2H, m), 4.19 (2H, t, J = 6.5 Hz), 3.03 (2H, s), 2.98 (2H, t, J = 6.4 Hz), 2.47-2.40 (2H, m), 2.37 (3H, s), 2.10-2.01 (2H, m), 1.95-1.81 (2H, m).	HR Calcd for $C_{25}H_{23}NO_4F_4$ $(M+H)^+$ 478.1636. Found 478.1624. For LR 478 $(M+H)^+$	
C-25		($CDCl_3$, 300 MHz) 8.06-8.05 (1H, d), 7.80-7.77 (1H, m), 7.50-7.47 (1H, d), 7.09-7.06 (2H, m), 6.80-6.77 (2H, m), 4.19 (2H, t, J = 6.5 Hz), 3.03 (2H, s), 2.94 (2H, t, J = 6.5 Hz), 2.44-2.38 (2H, m), 2.35 (3H, s), 2.08-2.01 (2H, m), 1.92-1.84 (2H, m).	HR Calcd for $C_{24}H_{23}NO_4Cl_2$ $(M+H)^+$ 460.1077. Found 460.1089. For LR 461 $(M+H)^+$	

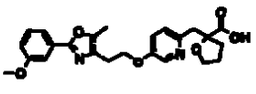
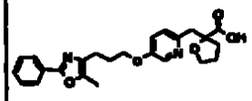
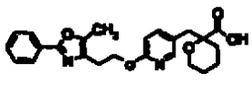
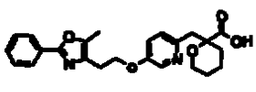
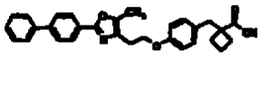
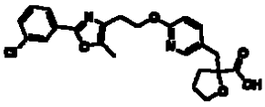
C-26		($CDCl_3$, 300 MHz) 7.87-7.85 (2H,m), 7.24-7.21 (2H, m), 7.09-7.07 (2H, m), 6.81-6.78 (2H, m), 4.20-4.17 (2H, m), 3.04 (2H, s), 2.96-2.94 (2H, m), 2.48-2.41 (2H, m), 2.38 (3H, s), 2.35 (3H, s), 2.10-2.02 (2H, m), 1.90-1.83 (2H, m).	HR Calcd for $C_{25}H_{27}NO_4$ $(M+H)^+$ 406.2013. Found 406.2014 For LR 406 $(M+H)^+$	
C-27		($CDCl_3$, 300 MHz) 7.91-7.88 (2H, m), 7.40-7.37 (2H, m), 7.09-7.06 (2H, m), 6.80-6.77 (2H, m), 4.18 (2H, t, J = 6.5 Hz), 3.03 (2H, s), 2.95 (2H, t, J = 6.5 Hz), 2.44-2.41 (2H, m), 2.35 (3H, s), 2.08-2.01 (2H, m), 1.90-1.87 (2H, m).	HR Calcd for $C_{24}H_{24}NO_4Cl$ $(M+H)^+$ 426.1467. Found 426.1471. For LR 426 $(M+H)^+$	
C-28		($CDCl_3$, 300 MHz) 7.92-7.89 (2H, m), 7.10-7.07 (2H, m), 6.95-6.92 (2H, m), 6.80-6.77 (2H, m), 4.17 (2H, t, J = 6.5 Hz), 3.85 (3H, s), 3.04 (2H, s), 2.95 (2H, t, J = 6.5 Hz), 2.48-2.38 (2H, m), 2.34 (3H, s), 2.10-2.02 (2H, m), 1.94-1.83 (2H, m).	HR Calcd for $C_{25}H_{27}NO_5$ $(M+H)^+$ 422.1962. Found 422.1948. For LR 423 $(M+H)^+$	
C-29		($CDCl_3$, 300 MHz) 7.57-7.55 (1H, m), 7.51-7.49 (1H, m), 7.35-7.30 (1H, m), 7.10-7.07 (2H, m), 6.97-6.93 (1H, m), 6.81-6.78 (2H, m), 4.19 (2H, t, J = 6.5 Hz), 3.87 (3H,s), 3.04 (2H, s), 2.96 (2H, t, J = 6.5 Hz), 2.48-2.38 (2H, m), 2.36 (3H, s), 2.11-2.02 (2H, m), 1.94-1.86 (2H, m).	HR Calcd for $C_{25}H_{27}NO_5$ $(M+H)^+$ 422.1962. Found 422.1947. For LR 422 $(M+H)^+$	
C-30		($CDCl_3$, 400 MHz) 8.23 (1H, s), 8.15-8.13 (1H, m), 7.64-7.63 (1H, m), 7.54-7.50 (1H, m), 7.07-7.05 (2H, m), 6.99-6.96 (1H, m), 6.77-6.75 (2H, m), 6.70-6.68 (1H, m), 4.19 (2H, t, J = 6.5 Hz).	HR Calcd for $C_{25}H_{24}NO_4F_3$ $(M+H)^+$ 460.1730. Found 460.1728. For LR 460 $(M+H)^+$	

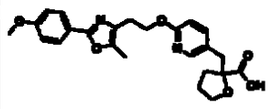
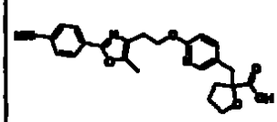
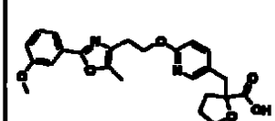
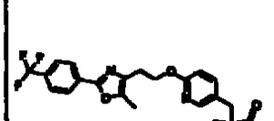
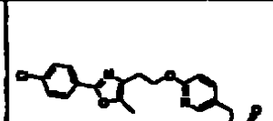
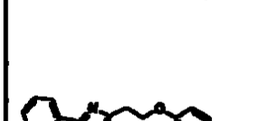
C-31		($CDCl_3$, 300 MHz) 7.96 (1H, s), 7.86-7.83 (1H, m), 7.36-7.33 (2H, m), 7.09-7.06 (2H, m), 6.79-6.76 (2H, m), 4.18 (2H, t, J = 6.5 Hz), 3.03 (2H, s), 2.95 (2H, t, J = 6.5 Hz), 2.47-2.38 (2H, m), 2.35 (3H, s), 2.08-2.01 (2H, m), 1.91-1.84 (2H, m).	HR Calcd for $C_{24}H_{24}NO_4Cl$ $(M+H)^+$ 426.1467. Found 426.1465. For LR 426 $(M+H)^+$	
C-32		($CDCl_3$, 400 MHz) 7.81 1H, s), 7.77-7.75 (1H, m), 7.33-7.29 (1H, m), 7.22-7.20 (1H, m), 7.09-7.07 (2H, m), 6.81-6.78 (2H, m), 4.19 (2H, t, J = 6.5 Hz), 3.04 (2H, s), 2.96 (2H, t, J = 6.5 Hz), 2.44-2.42 (2H, m), 2.39 (3H, s), 2.35 (3H, s), 2.08-2.03 (2H, m), 1.89-1.87 (2H, m).	HR Calcd for $C_{25}H_{27}NO_4$ $(M+H)^+$ 406.2013. Found 406.2026. For LR 407 $(M+H)^+$	
C-33		($CDCl_3$, 400 MHz) 8.08-8.06 (2H, d), 7.68-7.66 (2H, d), 7.09-7.07 (2H, m), 6.80-6.78 (2H, m), 4.91 (2h, t, J = 6.5 Hz), 3.03 (2H, s), 2.97 (2H, t, J = 6.5 Hz), 2.46-2.38 (2H, m), 2.37 (3H, s), 2.09-2.02 (2H, m), 1.92-1.82 (2H, m).	HR Calcd for $C_{25}H_{24}NO_4F_3$ $(M+H)^+$ 460.1730. Found 460.1723. For LR 461 $(M+H)^+$	
C-34		($DMSO-d_6$, 300 MHz) 12.19 (1H, s), 8.12-8.11 (2H, m), 7.82-7.79 (2H, m), 7.59-7.44 (6H, m), 7.13-6.98 (4H, m), 5.17 (2H, s), 2.97 (2H, s), 2.30-2.21 (2H, m), 2.01-1.73 (4H, m).	Calcd for $C_{28}H_{26}NO_4$ 440.1857. Found: 440.1846.	
C-35		($CDCl_3$, 300 MHz) 8.09-8.07 (2H, m), 7.68-7.66 (2H, m), 7.46-7.26 (6H, m), 7.10-6.78 (4H, m), 4.01 (2H, t, J = 5.8 Hz), 3.04-3.00 (4H, m), 2.49-2.39 (2H, m), 2.30-2.21 (2H, m), 2.11-2.02 (2H, m), 1.94-1.81 (2H, m).	Calcd for $C_{30}H_{30}NO_4$ 468.2107. Found: 468.2165.	
C-36		($DMSO-d_6$, 300 MHz) 12.92 (1H, s), 8.12-8.09 (2H, m), 7.82-7.79 (2H, m), 7.60-7.44 (6H, m), 7.02-6.99 (2H, m), 6.64-6.60 (2H, m), 5.13 (2H, s), 2.68-2.59 (2H, m), 2.37-2.26 (2H, m), 1.95-1.84 (2H, m).	Calcd for $C_{27}H_{24}NO_5$ 442.1649. Found: 442.1639.	

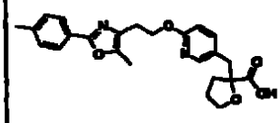
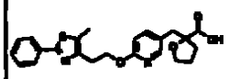
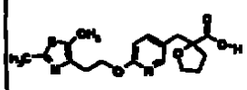
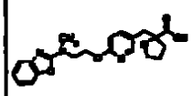
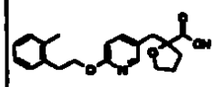
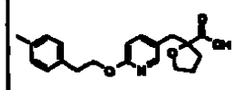
C-37		($CDCl_3$, 300 MHz) 8.10-8.06 (2H, m), 7.89-7.86 (2H, m), 7.48-7.32 (6H, m), 6.79-6.66 (4H, m), 3.91 (2H, t, J = 6.0 Hz), 2.98 (2H, t, J = 7.3 Hz), 2.80-2.71 (2H, m), 2.50-2.40 (2H, m), 2.24-2.15 (2H, m), 2.06-1.93 (2H, m).	Calcd for $C_{29}H_{28}NO_4$ 470.1962. Found: 470.1952.	Calcd for $C_{29}H_{27}NO_5$ C 74.18, H 5.80, N 2.98. Found: C 73.07, H 6.81, N 2.43.
C-38		($CDCl_3$, 300 MHz) 8.08-8.07 (2H, m), 7.88-7.86 (2H, m), 7.46-7.28 (6H, m), 7.10-6.78 (4H, m), 4.01 (2H, t, J = 5.8 Hz), 3.04-3.00 (4H, m), 2.49-2.39 (2H, m), 2.30-2.21 (2H, m), 2.11-2.02 (2H, m), 1.94-1.81 (2H, m)	HR Calcd for $C_{29}H_{28}NO_4$ $(M+H)^+$ 468.2107. Found 468.2165. For LR 468 $(M+H)^+$	
C-39		($CDCl_3$, 400 MHz) 8.03 (2H, d, J = 8.3 Hz), 7.86 (2H, d, J = 8.3 Hz), 7.65-7.60 (2H, m), 7.49-7.32 (3H, m), 6.74-6.63 (4H, m), 4.03 (2H, t, J = 6.6 Hz), 2.96 (2H, t, J = 6.6 Hz), 2.81-2.70 (2H, m), 2.49-2.35 (2H, m), 2.38 (3H, s), 2.10-1.90 (2H, m).	Calcd for $C_{29}H_{28}NO_5$ 470.1962. Found: 470.1948.	Calcd for $C_{29}H_{27}NO_5$ C 74.18, H 5.80, N 2.98. Found: C 74.07, H 5.83, N 2.89.
C-40		($CDCl_3$, 400 MHz) 8.00-7.93 (2H, m), 7.46-7.40 (3H, m), 6.73-6.62 (4H, m), 4.02 (2H, t, J = 6.6Hz), 2.94 (2H, t, J = 6.6Hz), 2.80-2.69 (2H, m), 2.47-2.33 (2H, m), 2.36 (3H, s), 2.10-1.88 (2H, m).	Calcd for $C_{23}H_{24}NO_5$ 394.1649. Found: 394.1639.	Calcd for $C_{23}H_{23}NO_5$ C 70.21, H 5.89, N 3.56. Found: C 69.87, H 6.05, N 3.47.
C-41		($CDCl_3$, 400 MHz) 8.01-7.94 (2H, m), 7.47-7.39 (3H, m), 6.82-6.65 (4H, m), 3.87 (2H, d, J = 6.0Hz), 2.82-2.71 (2H, m), 2.67-2.60 (2H, m), 2.50-2.38 (2H, m), 2.29 (3H, s), 2.10-1.90 (4H, m).	for LR 408 $(M+H)^+$	Calcd for $C_{24}H_{25}NO_5$ C 70.74, H 6.18, N 3.44. Found: C 70.52, H 6.19, N 3.41.

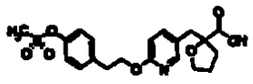
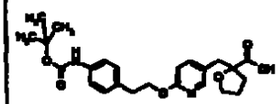
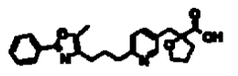
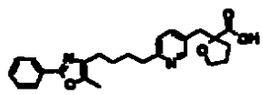
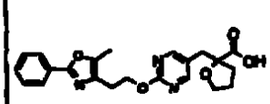
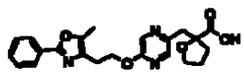
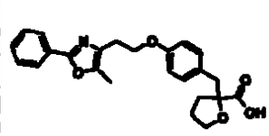
C-42		($CDCl_3$, 400 MHz) 8.04-7.97 (2H, m), 7.47-7.40 (3H, m), 6.66-6.63 (4H, m), 4.90 (2H, s), 2.78-2.70 (2H, m), 2.47-2.35 (2H, m), 2.41 (3H, s),.2.10-1.90(2H, m).	for LR 380 $(M+H)^+$	Calcd for $C_{22}H_{21}NO_5$ C 69.64, H 5.58, N 6.69. Found: C 69.49, H 5.68, N 3.62.
C-43		($MeOH-d_4$, 400 MHz) 7.87-7.84 (3H, m), 7.46 (1H, dd, J = 2.3, 8.6 Hz), 7.39-7.35 (3H, m), 6.57 (1H, d, J = 8.6 Hz), 4.38 (2H, t, J = 6.7 Hz), 2.88 (4H, m), 2.25 (3H, s), 2.29-2.20 (2H, m), 1.88-1.81 (2H, m), 1.75-1.68 (2H, m).	Calcd for $C_{23}H_{24}N_2O_4$ 393.1809. Found: 393.1815.	
C-44		(DMSO-d_6, 300 MHz) 8.02 (1H, d, J = 2.1 Hz), 7.91-7.88 (2H, m), 7.60 (1H, dd, J = 2.3, 8.5 Hz), 7.52-7.47 (3H, m), 6.72 (1H, d, J = 8.7 Hz), 5.66 (1H, bs), 4.73 (1H, s), 4.45 (2H, t, J = 6.8 Hz), 2.90 (2H, t, J = 6.7 Hz), 2.40-2.16 (2H, m), 2.30 (3H, s), 2.14-2.02 (2H, m), 1.75-1.63 (1H, m), 1.56-1.42 (1H, m).	for LR 408 $(M)^-$	Calcd for $C_{23}H_{24}N_2O_5$ C 67.63, H 5.92, N 6.86. Found:C 67.51, H 6.08, N 6.75.
C-45		(Methyl sulfoxide-d_6, 400 MHz): 8.02 (1H, d, J = 2.1 Hz), 7.91-7.88 (2H, m), 7.60 (1H, dd, J = 2.3, 8.5 Hz), 7.52-7.47 (3H, m), 6.72 (1H, d, J = 8.7 Hz), 4.68 (1H, s), 4.45 (2H, t, J = 6.8 Hz), 4.01 (2H, q, J = 7.1 Hz), 2.90 (2H, t, J = 6.7 Hz), 2.40-2.16 (2H, m), 2.30 (3H, s), 2.14-2.02 (2H, m), 1.75-1.63 (1H, m), 1.56-1.42 (1H, m), 1.29 (3H, t, J = 7.2 Hz)	for LR 437 $(M+H)^+$	
C-46		($CDCl_3$, 400 MHz) 8.00-7.93 (3H, m), 7.42-7.37 (4H, m), 6.63 (1H, d, J = 8.5 Hz), 4.48 (2H, t, J = 6.6 Hz), 2.98 (2H, t, J = 6.7 Hz), 2.86 (2H, s), 2.31 (3H, s), 2.10-2.02 (2H, m), 1.66-1.50 (6H, m).	for LR 406 $(M)^-$	
C-47		($CDCl_3$, 400 MHz) 7.97-7.93 (3H, m), 7.43-7.33 (4H, m), 6.63 (1H, d, J = 8.5 Hz), 4.48 (2H, t, J = 6.6 Hz), 2.95 (2H, t, J = 6.6 Hz), 2.73 (2H, s), 2.30 (3H, s), 2.01 (2H, d, J = 12.6 Hz), 1.59-1.50 (3H, m), 1.40-1.15 (5H, m).	for LR 420 $(M)^-$	

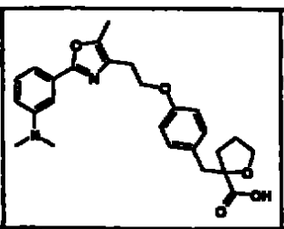
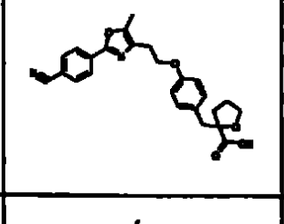
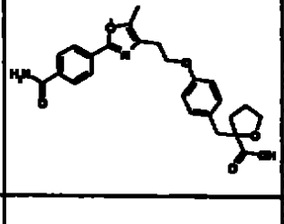
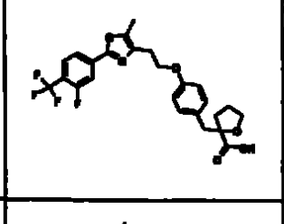
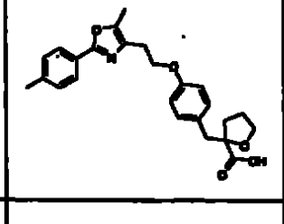
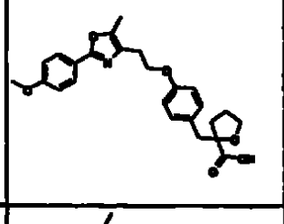
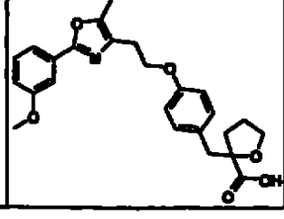
C-48		($CDCl_3$, 400 MHz) 7.99-7.94 (3H, m), 7.49 (1H, dd, J = 2.4, 8.6 Hz), 7.44-7.38 (3H, m), 6.63 (1H, d, J = 8.5 Hz), 4.50 (2H, t, J = 6.7 Hz), 4.00-3.93 (1H, m), 3.89-3.81 (1H, m), 3.14 (1H, d, J = 14.1 Hz), 2.95 (2H, t, J = 6.7 Hz), 2.85 (1H, d, J = 14.1 Hz), 2.31 (3H, s), 1.99-1.73 (4H, m).	for LR 409 $(M)^+$	
C-49		(MeOH-d_4, 300 MHz) 8.37 (1H, d, J = 2.6 Hz), 8.07 (1H, dd, J = 2.6, 8.9 Hz), 7.93-7.90 (2H, m), 7.79 (1H, d, J = 8.9 Hz), 7.47-7.40 (3H, m), 4.41 (2H, t, J = 6.2 Hz), 3.92-3.86 (2H, m), 3.05 (2H, t, J = 6.2 Hz), 2.36 (3H, s), 3.50 (1H, d, J = 14.3 Hz), 3.15 (1H, d, J = 14.3 Hz), 2.31-2.23 (1H, m), 2.00-1.92 (1H, m), 1.89-1.73 (2H, m).	for LR 408 $(M)^-$	Calcd for $C_{23}H_{25}N_2O_5Cl$ C 62.09, H 5.66, N 6.30. Found: C 61.96, H 5.75, N 6.18.
C-50		(MeOD, 400 MHz): 8.37 (1H, d, J = 2.6 Hz), 8.07 (1H, dd, J = 2.6, 8.9 Hz), 7.93-7.90 (2H, m), 7.79 (1H, d, J = 8.9 Hz), 7.47-7.40 (2H, m), 4.41 (2H, t, J = 6.2 Hz), 3.92-3.86 (2H, m), 3.50 (1H, d, J = 14.3 Hz), 3.15 (1H, d, J = 14.3 Hz), 3.05 (2H, t, J = 6.2 Hz), 2.36 (3H, s), 2.34 (3H, s), 2.31-2.23 (1H, m), 2.00-1.92 (1H, m), 1.89-1.73 (2H, m)	for LR 423 $(M+H)^+$	
C-51		(CDCl$_3$, 400 MHz): 8.03 (1H, d, J = 2.5 Hz), 7.77-7.74 (2H, m), 7.36-7.31 (4H, m), 7.26 (1H, d, J = 8.6 Hz), 4.31 (2H, t, J = 6.6 Hz), 3.81-3.69 (2H, m), 3.11 (2H, t, J = 6.4 Hz), 3.02 (1H, d, J = 13.9 Hz), 2.37 (3H, s), 2.36-2.34 (1H, m), 2.18-2.11 (1H, m), 1.94-1.87 (1H, m), 1.78-1.68 (1H, m), 1.60-1.53 (1H, m)	for LR 425 $(M+H)^+$	
C-52		(CDCl$_3$, 400 MHz): 8.04 (1H, d, J = 2.8 Hz), 7.85-7.83 (2H, m), 7.41-7.39 (2H, m), 7.33 (1H, dd, J = 8.6, 3.0 Hz), 7.27 (1H, d, J = 8.8 Hz), 4.23 (2H, t, J = 6.3 Hz), 3.82-3.70 (2H, m), 3.17-3.15 (1H, m), 3.03 (1H, d, J = 14.2 Hz), 2.91 (2H, t, J = 6.3 Hz), 2.29 (3H, s), 2.19-2.12 (1H, m), 1.96-1.88 (1H, m), 1.78-1.71 (1H, m), 1.61-1.54 (1H, m)	for LR 443 $(M+H)^+$	
C-53		(MeOD, 400 MHz): 8.01 (1H, d, J = 1.5 Hz), 7.80-7.77 (2H, m), 7.25-7.24 (2H, m), 6.93-6.91 (2H, m), 4.20 (2H, t, J = 6.3 Hz), 3.80-3.69 (2H, m), 3.75 (3H, s), 3.17-3.15 (1H, m), 3.01 (1H, d, J = 13.9 Hz), 2.88 (2H, t, J = 6.3 Hz), 2.26 (3H, s), 2.17-2.11 (1H, m), 1.94-1.87 (1H, m), 1.75-1.66 (1H, m), 1.58-1.49 (1H, m)	for LR 439 $(M+H)^+$	

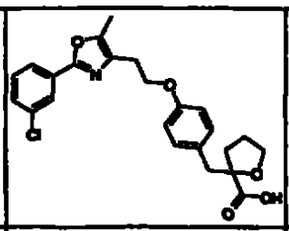
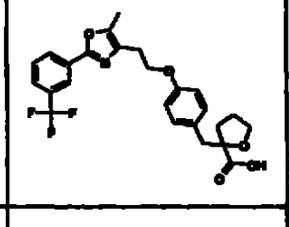
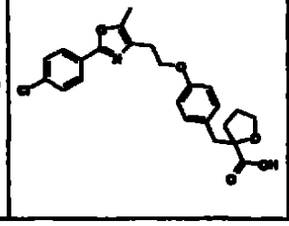
C-54		(MeOD, 400 MHz): 8.01 (1H, d, J = 2.3 Hz), 7.44-7.40 (2H, m), 7.30-7.22 (3H, m), 6.94-6.91 (1H, m), 4.21 (2H, t, J = 6.4 Hz), 3.80-3.67 (2H, m), 3.75 (3H, s), 3.21-3.17 (1H, m), 3.01 (1H, d, J = 13.9 Hz), 2.90 (2H, t, J = 6.4 Hz), 2.28 (3H, s), 2.17-2.11 (1H, m), 1.94-1.87 (1H, m), 1.77-1.67 (1H, m), 1.60-1.50 (1H, m)	for LR 439 $(M+H)^+$	
C-55		($CDCl_3$, 300 MHz): 8.43 (1H, d, J = 2.6 Hz), 7.97-7.93 (1H, m), 7.83-7.79 (1H, m), 7.60-7.52 (2H, m), 7.48-7.42 (3H, m), 4.14 (2H, t, J = 6.0 Hz), 4.06-3.99 (2H, m), 3.82 (1H, d, J = 13.9 Hz), 3.37 (1H, d, J = 13.9 Hz), 2.69 (2H, t, J = 6.0 Hz), 2.32 (3H, s), 2.23-1.96 (6H, m)	for LR 423 $(M+H)^+$	
C-56		($CDCl_3$, 300 MHz): 7.93-8.03 (3H, m), 7.83-7.79 (1H, m), 7.37-7.54 (4H, m), 6.85 (1H, m), 4.50 (2H, t, J = 6.0 Hz), 3.75 (2H, m), 2.95 (4H, m) 2.33 (3H, s) 2.12 (2H, m), 1.39-1.77 (5H, m)	for LR 423 $(M+H)^+$	
C-57		(MeOD, 400 MHz): 7.98 (1H, d, J = 2.8 Hz), 7.86-7.84 (2H, m), 7.39-7.36 (3H, m), 7.24 (1H, d, J = 8.8, 2.8 Hz), 7.19 (1H, d, J = 8.6 Hz), 4.21 (2H, t, J = 6.6 Hz), 3.70-3.66 (1H, m), 3.60-3.53 (1H, m), 2.95 (2H, s), 2.90 (2H, t, J = 6.4 Hz), 2.28 (3H, s), 2.07-2.01 (1H, m), 1.61-1.58 (1H, m), 1.40-1.32 (4H, m)	for LR 423 $(M+H)^+$	
C-58		(DMSO-d_6, 400 MHz) 8.17 (2H, d, J = 8.3 Hz), 7.99 (2H, d, J = 8.3 Hz), 7.92 (2H, d, J = 8.3 Hz), 7.68 (2H, t, J = 8.3 Hz), 7.58 (1H, t, J = 8.3 Hz), 7.24-7.02 (4H, m), 4.36 (2H, t, J = 6.6 Hz), 3.11 (2H, s), 3.11-3.07 (2H, m), 2.55 (3H, s), 2.44-2.37 (2H, m), 2.15-1.89 (4H, m).	Calcd for $C_{30}H_{30}NO_4$ 468.2170. Found: 468.2163.	Calcd for $C_{30}H_{30}NO_4.0.2H_2O$ C 76.47, H 6.29, N 2.97. Found: C 76.48, H 6.30, N 2.90.
C-59		^{1}H NMR (DMSO-d_6, 400 MHz) : 8.04 (2H, d, J = 8.3 Hz), 7.95-7.93 (3H, m), 7.53 (1H, dd, J = 8.6 and 2.3 Hz), 6.69 (1H, d, J = 8.3 Hz), 4.45 (2H, t, J = 6.6 Hz), 3.75 (2H, t, J = 6.8 Hz), 3.01 (1H, d, J = 13.9 Hz), 2.93 (2H, t, J = 6.6 Hz), 2.82 (1H, d, J = 14.2 Hz), 2.33 (3H, s), 2.13-2.07 (1H, m), 1.84-1.82 (3H, m)		Calcd for $C_{23}H_{24}ClN_2O_5$ 443.1368. Found: 443.1377

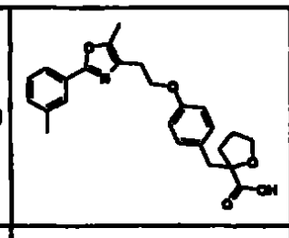
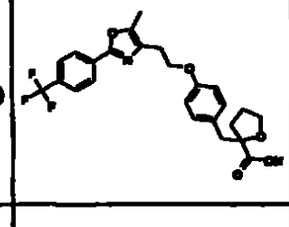
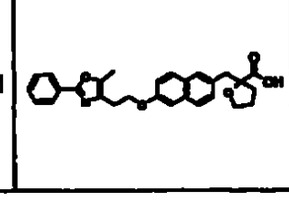
C-60		^{1}H NMR (DMSO-d_6, 400 MHz) : 12.45 (1H, s), 7.95 (1H, d, J = 2.3 Hz), 7.83 (2H, d, J = 8.8 Hz), 7.53 (1H, dd, J = 8.6 and 2.3 Hz), 7.03 (2H, d, J = 8.8 Hz), 6.69 (1H, d, J = 8.3 Hz), 4.42 (2H, t, J = 6.8 Hz), 3.80 (3H, s), 3.75 (2H, t, J = 6.8 Hz), 3.01 (1H, d, J = 13.9 Hz), 2.87 (2H, t, J = 6.8 Hz), 2.82 (1H, d, J = 14.2 Hz), 2.28 (3H, s), 2.14-2.07 (1H, m), 1.83-1.63 (3H, m)		Calcd for $C_{24}H_{27}N_2O_6$ 439.1864. Found: 439.1874
C-61		^{1}H NMR (DMSO-d_6, 400 MHz): 8.04 (2H, d, J = 8.3 Hz), 7.95-7.93 (3H, m), 7.53 (1H, dd, J = 8.6 and 2.3 Hz), 6.69 (1H, d, J = 8.3 Hz), 4.45 (2H, t, J = 6.6 Hz), 3.75 (2H, t, J = 6.8 Hz), 3.01 (1H, d, J = 13.9 Hz), 2.93 (2H, t, J = 6.6 Hz), 2.82 (1H, d, J = 14.2 Hz), 2.33 (3H, s), 2.13-2.07 (1H, m), 1.84-1.62 (3H, m)		Calcd for $C_{24}H_{24}N_3O_5$ 434.1711. Found: 434.1705
C-62		^{1}H NMR (DMSO-d_6, 400 MHz) : 7.95 (1H, d, J = 2.0 Hz), 7.53 (1H, dd, J = 8.3 and 2.3 Hz), 7.48 (1H, d, J = 7.8 Hz), 7.42-7.38 (2H, m), 7.04 (1H, dd, J = 8.3 and 2.5 Hz), 6.69 (1H, d, J = 8.3 Hz), 4.43 (2H, t, J = 6.6 Hz), 3.81 (3H, s), 3.75 (2H, t, J = 6.8 Hz), 3.01 (1H, d, J = 13.9 Hz), 2.90 (2H, t, J = 6.6 Hz), 2.82 (1H, d, J = 13.9 Hz), 2.31 (3H, s), 2.13-2.07 (1H, m), 1.83-1.58 (3H, m)		Calcd for $C_{24}H_{27}N_2O_6$ 439.1864. Found: 439.1874
C-63		^{1}H NMR (DMSO-d_6, 400 MHz) : 12.51 (1H, s), 8.10 (2H, d, J = 8.1 Hz), 7.95 (1H, d, J = 2.0 Hz), 7.85 (2H, d, J = 8.3 Hz), 7.53 (1H, dd, J = 8.3 and 2.3 Hz), 6.69 (1H, d, J = 8.6 Hz), 4.45 (2H, t, J = 6.8 Hz), 3.75 (2H, t, J = 6.6 Hz), 3.01 (1H, d, J = 13.9 Hz), 2.93 (2H, t, J = 6.8 Hz), 2.82 (1H, d, J = 13.9 Hz), 2.34 (3H, s), 2.13-2.06 (1H, m), 1.84-1.60 (3H, m)	Calcd for $C_{24}H_{24}F_3N_2O_5$ 477.1632. Found: 477.1635	
C-64		^{1}H NMR ($CDCl_3$, 400 MHz) : 8.16 (1H, s), 7.88 (2H, d, J = 8.6 Hz), 7.81 (1H, d, J = 8.6 Hz), 7.41 (2H, d, J = 8.6 Hz), 6.87 (1H, d, J = 8.6 Hz), 4.51 (2H, t, J = 6.1 Hz), 4.03-3.90 (2H, m), 3.23 (1H, d, J = 14.2 Hz), 3.04 (2H, t, J = 6.1 Hz), 2.86 (1H, d, J = 14.2 Hz), 2.42-2.35 (1H, m), 2.37 (3H, s), 2.01-1.87 (3H, m)	for LR 443 $(M+H)^+$	
C-65		^{1}H NMR (DMSO-d_6, 400 MHz) : 7.95 (1H, d, J = 2.0 Hz), 7.73 (1H, s), 7.69 (1H, d, J = 7.3 Hz), 7.51 (1H, dd, J = 8.6 and 2.3 Hz), 7.37 (1H, t, J = 7.8 Hz), 7.28 (1H, d, J = 7.1 Hz), 6.69 (1H, d, 8.3 Hz), 4.43 (2H, t, J = 6.8 Hz), 3.75 (2H, t, J = 6.6 Hz), 3.01 (1H, d, J = 14.2 Hz), 2.89 (2H, t, J = 6.8 Hz), 2.82 (1H, d, J = 14.2 Hz), 2.36 (3H, s), 2.30 (3H, s), 2.14-2.08 (1H, m), 1.84-1.60 (3H, m)	Calcd for $C_{24}H_{27}N_2O_6$ 423.1915. Found: 423.1927.	Calcd for $C_{24}H_{26}N_2O_5 0.4H_2O$ C 64.23 H 6.01 N 6.19. Found: C 64.16 H 6.16 N 6.01

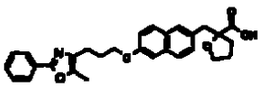
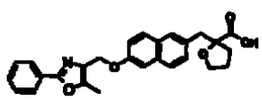
C-66		^{1}H NMR (DMSO-d_6, 400 MHz) : 7.95 (1H, d, J = 2.3 Hz), 7.79 (2H, d, J = 8.1 Hz), 7.53 (1H, dd, J = 8.3 and 2.5 Hz), 7.29 (2H, d, J = 8.1 Hz), 6.68 (1H, d, 8.3 Hz), 4.43 (2H, t, J = 7.1 Hz), 3.75 (2H, t, J = 6.8 Hz), 3.01 (1H, d, J = 13.9 Hz), 2.88 (2H, t, J = 6.8 Hz), 2.82 (1H, d, J = 13.9 Hz), 2.34 (3H, s), 2.29 (3H, s), 2.14-2.07 (1H, m), 1.84-1.80 (3H, m)	Calcd for $C_{24}H_{27}N_2O_5$ 423.1915. Found: 423.1929.	Calcd for $C_{24}H_{26}N_2O_5 0.9H_2O$ C 65.71 H 6.39 N 6.39. Found: C 65.61 H 6.34 N 6.20
C-67		^{1}H NMR (MeOH-d_4, 400 MHz): 8.28 (1 H, s) 7.76 (2 H, dt, J=7.7, 0.2 Hz) 7.56 (1 H, d, J=9.1 Hz) 7.34 - 7.39 (1 H, m) 7.14 - 7.20 (2 H, m) 6.28 (1 H, d, J=9.2 Hz) 4.12 (2 H, t, J=8.0 Hz) 3.70 - 3.84 (2 H, m) 3.14 - 3.20 (1 H, m) 3.00 - 3.06 (1 H, m) 2.75 (2 H, t, J=8.0 Hz) 2.34 - 2.44 (1 H, m) 2.26 - 2.31 (3 H, m) 1.82 - 2.05 (3 H, m)	LRMS: 426 $(M+H)^+$.	
C-68		^{1}H NMR (MeOH-d_4, 400 MHz): 8.28 (1 H, s) 7.56 (1 H, d, J=9.1 Hz) 6.28 (1 H, d, J=9.2 Hz) 4.12 (2 H, t, J=8.0 Hz) 3.70 - 3.84 (2 H, m) 3.14 - 3.20 (1 H, m) 2.99 - 3.06 (1 H, m) 2.58 (2 H, t, J=8.0 Hz) 2.48 (3 H, s) 2.31 - 2.44 (1 H, m) 2.18 (3 H, s) 1.81 - 2.05 (3 H, m)	for LR 384 $(M+H)^+$	
C-69		^{1}H NMR (MeOH-d_4, 400 MHz): 8.19 (1 H, s) 7.45 (2 H, dd, J=9.0, 8.4 Hz) 7.33 (1 H, d, J=7.7 Hz) 7.15 - 7.21 (1 H, m) 6.99 - 7.05 (1 H, m) 6.24 (1 H, d, J=9.2 Hz) 4.02 (2 H, t, J=5.2 Hz) 3.70 - 3.84 (2 H, m) 3.42 (2 H, t, J=5.2 Hz) 3.14 - 3.20 (1 H, m) 2.99 - 3.06 (1 H, m) 2.93 (3 H, s) 2.34 - 2.43 (1 H, m) 1.82 - 2.05 (3 H, m)	for LR 398 $(M+H)^+$	
C-70		^{1}H NMR (MeOH-d_4, 400 MHz): 8.28 (1 H, s) 7.56 (1 H, d, J=9.1 Hz) 7.08 - 7.20 (4 H, m) 6.28 (1 H, d, J=9.2 Hz) 4.50 (2 H, t, J=6.9 Hz) 3.70 - 3.84 (2 H, m) 3.14 - 3.20 (1 H, m) 3.00 - 3.05 (1 H, m) 2.90 (2 H, t, J=6.9 Hz) 2.32 - 2.43 (1 H, m) 2.28 (3 H, s) 1.81 - 2.05 (3 H, m)	for LR 342 $(M+H)^+$	
C-71		^{1}H NMR (MeOH-d_4, 400 MHz): 8.28 (1 H, s) 7.56 (1 H, d, J=9.1 Hz) 7.09 - 7.15 (4 H, m) 6.28 (1 H, d, J=9.2 Hz) 4.57 (2 H, t, J=6.5 Hz) 3.70 - 3.84 (2 H, m) 3.28 (2 H, t, J=6.5 Hz) 3.14 - 3.20 (1 H, m) 3.00 - 3.06 (1 H, m) 2.34 - 2.44 (1 H, m) 2.27 - 2.31 (3 H, m) 1.82 - 2.05 (3 H, m)	for LR 342 $(M+H)^+$	

C-72		^{1}H NMR ($CDCl_3$, 400 MHz): 8.2-8.6 (1H, br s), 8.10 (1 H, s) 7.58 (1 H, d, *J*=9.1 Hz) 6.85-7.25 (4 H, m) 6.70 (1 H, d, *J*=9.2 Hz) 3.80-4.05 (2H, *m*), 3.63 (2 H, t, *J*=6.5 Hz) 3.35 (3H, s), 2.85 (2 H, t, *J*=6.5 Hz) 2.30 (1H, m) 1.65-2.05 (3H, m)		
C-73		^{1}H NMR ($CDCl_3$, 400 MHz): 7.98 (1H, s) 7.48 (1 H, d, *J*=9.1 Hz) 7.15-7.30 (4 H, m) 6.65 (2 H, m) 4.37 (2 H, t, *J*=6.5 Hz) 3.80-4.03 (2H, m), 2.80-3.20 (4H, m) 2.35 (3H, m) 1.70-2.05 (3H, m) 1.50 (9H, s)		
C-74		(Acetone-d_6, 300 MHz): 8.37 (1H, d, *J* = 1.9 Hz), 7.96 (2H, m), 7.56 (1H, dd, *J* = 7.9, 2.3 Hz), 7.45 (3H, m), 7.14 (1H, d, *J* = 7.9 Hz), 3.89 (2H, m), 3.05 (2H, m), 2.77 (2H, m), 2.50 (2H, t, *J* = 7.4 Hz), 2.30 (3H, s) 2.16 (2H, *m*), 1.86 (4H, *m*)	for LR 405 $(M)^-$	
C-75		(MeOD, 400 MHz): 8.19 (1H, s), 7.82-7.80 (2H, m), 7.61 (1H, dd, *J* = 7.6, 1.8 Hz), 7.35-7.33 (3H, m), 7.15 (1H, d, *J* = 8.1 Hz), 3.83-3.73 (2H, m), 3.09 (1H, d, *J* = 13.9 Hz), 2.82 (1H, d, *J* = 13.9 Hz), 2.69 (2H, t, *J* = 7.2 Hz), 2.41 (2H, t, *J* = 6.7 Hz), 2.23-2.13 (1H, m), 2.20 (3H, s), 1.88-1.79 (1H, m), 1.78-1.53 (6H, m)	for LR 421 $(M+H)^+$	
C-76		(MeOD, 300 MHz): 8.34-8.32 (2H, bm), 7.87-7.85 (2H, bm), 7.8-7.36 (3H, bm), 4.54 (2H, bs), 3.83 (2H, bs), 3.08 (1H, d, *J* = 10.7 Hz), 2.93-2.89 (1H, bm), 2.80 (1H, d, *J* = 10.7 Hz), 2.24 (3H, s), 1.92-1.77 (5H, m)	for LR 410 $(M+H)^+$	
C-77		(Acetone-d_6, 400 MHz): 8.08 (1H, s), 7.95 (2H, m), 7.46 (3H, m), 4.57 (2H, t, *J* = 6.5 Hz), 3.83 (2H, m), 3.10 (4H, *m*), 2.36 (3H, s), 2.20 (2H, d, *J* = 7.0 Hz), 1.75 (2H, m)	for LR 408 $(M)^-$	
C-78		^{1}H NMR (DMSO-d_6, 400 MHz) : 12.40 (1H, s), 7.90 (2H, dd, *J* = 7.8 and 1.8 Hz), 7.51-7.44 (3H, m), 7.10 (2H, d, *J* = 8.3 Hz), 6.81 (2H, d, *J* = 8.6), 4.16 (2H, t, *J* = 6.8 Hz), 3.73 (2H, t, *J* = 6.8 Hz), 2.99 (1H, d, *J* = 13.9 Hz), 2.90 (2H, t, *J* = 6.6 Hz), 2.81 (1H, d, *J* = 13.9 Hz), 2.34 (3H, s), 2.11-2.04 (1H, m), 1.82-1.57 (3H, m).	Calcd for $C_{24}H_{28}NO_6$ 426.1806. Found: 408.1797.	Calcd for $C_{24}H_{25}NO_5$ C 70.75 H 6.18 N 3.44. Found: C 70.53 H 6.18 N 3.31

C-79		(DMSO-d_6, 400 MHz) 7.25-7.24 (1H, m), 7.19-7.17 (2H, m), 7.06-7.04 (2H, m), 6.76-6.75 (1H, m), 6.72-6.70 (2H, m), 4.11 (2H, t, J = 6.5 Hz), 3.77-3.71 (2H, m), 3.00-2.96 (1H, m), 2.89 (6H, s), 2.87-2.85 (2H, m), 2.84-2.76 (1H, m), 2.98 (3H, s), 2.12-2.10 (1H, m), 1.85-1.82 (1H, m), 1.71-1.58 (2H, m)	HR Calcd for $C_{28}H_{30}N_2O_5$ $(M+H)^+$ 451.2228. Found 451.2213. For LR 451 $(M+H)^+$	
C-80		(DMSO-d_6, 300 MHz) 12.40 (1H, s), 8.14-8.11 (2H, m), 8.03-8.04 (2H, m), 7.19-7.16 (2H, m), 6.89-6.86 (2H, m), 4.24 (2H, t, J = 6.5 Hz), 3.80 (2H, t, J = 6.6 Hz), 3.09-3.04 (1H, m), 3.00 (2H, t, J = 6.4 Hz), 2.91-2.86 (1H, m), 2.45 (3H, s), 2.19-2.13 (1H, m), 1.88-1.67 (3H, m)	HR Calcd for $C_{28}H_{24}N_2O_5$ $(M+H)^+$ 433.1758. Found 433.1741. For LR 433 $(M+H)^+$	
C-81		(DMSO-d_6, 300 MHz) 8.10 (1H, s), 8.03-7.96 (4H, m), 7.48 (1H, s), 7.15-7.12 (2H, m), 6.85-6.83 (2H, m), 4.20 (2H, t, J = 6.5 Hz), 3.76 (2H, t, J = 6.5 Hz), 3.04-3.00 (1H, m), 2.95 (2H, t, J = 6.5 Hz), 2.88-2.82 (1H, m), 2.39 (3H, s), 2.12 (1H, m), 1.83-1.80 (3H, m)	For LR 451 $(M+H)^+$	
C-82		($CDCl_3$, 300 MHz) 7.85-7.77 (2H, m), 7.68-7.63 (1H, m), 7.15-7.12 (2H, m), 6.82-6.80 (2H, m), 4.22 (2H, t, J = 6.5 Hz), 4.01-3.96 (1H, m), 3.90-3.85 (1H, m), 3.19-3.14 (1H, m), 2.97 (2H, t, J = 6.5 Hz), 2.90-2.85 (1H, m), 2.39 (3H, s), 2.36-2.32 (1H, m), 2.06-1.96 (1H, m), 1.87-1.77 (2H, m).	HR Calcd for $C_{28}H_{23}NO_5F_4$ $(M+H)^+$ 494.1585. Found 494.1579. For LR 494 $(M+H)^+$	
C-83		($CDCl_3$, 400 MHz) 7.87-7.84 (2H, d), 7.23-7.21 (2H, d), 7.14-7.12 (2H, d), 6.82-6.80 (2H, d), 4.19 (2H, t, J = 6.5 Hz), 4.01-3.94 (1H, m), 3.87-3.81 (1H, m), 3.17-3.14 (1H, m), 2.95 (2H, t, J = 6.5 Hz), 2.90-2.87 (1H, m), 2.38 (3H, s), 2.35 (3H, s), 2.33-2.30 (1H, m), 2.03-1.95 (1H, m), 1.87-1.72 (2H, m).	For LR 422 $(M+H)^+$	
C-84		($CDCl_3$, 400 MHz) 7.92-7.90 (2H, m), 7.12-7.10 (2H, m), 6.94-6.92 (2H, m), 6.80-6.78 (2H, m), 4.18 (2H, t, J = 6.5 Hz), 4.02-3.97 (2H, m), 3.84 (3H, s), 3.17-3.13 (1H, m), 2.95 (2H, t, J = 6.5 Hz), 2.90-2.86 (1H, m), 2.35 (3H, s), 2.03-2.00 (2H, m), 1.87-1.81 (2H, m).	HR Calcd for $C_{29}H_{27}NO_5$ $(M+H)^+$ 438.1911. Found 438.1913. For LR 438 $(M+H)^+$	
C-85		($CDCl_3$, 400 MHz) 7.57-7.55 (1H, m), 7.51-7.49 (1H, m), 7.35-7.30 (1H, m), 7.10-7.07 (2H, m), 6.97-6.93 (1H, m), 6.81-6.78 (2H, m), 4.19 (2H, t, J = 6.5 Hz), 3.87 (3H, s), 3.04 (2H, s), 2.96 (2H, t, J = 6.5 Hz), 2.48-2.38 (2H, m) 2.36 (2H, s), 2.11-2.02 (2H, m), 1.94-1.85 (2H, m).		

C-86		($CDCl_3$, 400 MHz) 7.97 (1H, s), 7.86-7.84 (1H, m), 7.37-7.35 (2H, m), 7.15-7.12 (2H, m), 6.82-6.80 (2H, m), 4.20 (2H, t, J = 6.5 Hz), 3.99-3.95 (1H, m), 3.88-3.84 (1H, m), 3.18-3.14 (1H, m), 2.98 (2H, t, J = 6.5 Hz), 2.90-2.87 (1H, m), 2.37 (3H, s), 2.36-2.31 (1H, m), 2.01-1.98 (1H, m), 1.88-1.73 (2H, m).		
C-87		$CDCl_3$, 400 MHz) 8.24 (1H, s), 8.15-8.14 (1H, m), 7.86-7.84 (1H, m), 7.57-7.54 (1H, m), 7.15-7.13 (2H, m), 6.82-6.80 (2H, m), 4.21 (2H, t, J = 6.5 Hz), 3.88-3.84 (2H, m), 3.18-3.15 (1H, m), 2.97 (2H, t, J = 6.5 Hz), 2.90-2.88 (1H, m), 2.39 (3H, s), 2.01-1.98 (2H, m), 1.85-1.81 (2H, m).	HR Calcd for $C_{25}H_{24}NO_5F_3$ $(M+H)^+$ 476.1680. Found 476.1687. For LR 477 $(M+H)^+$	
C-88		($CDCl_3$, 400 MHz) 7.91-7.89 (2H, m), 7.40-7.38 (2H, m), 7.14-7.13 (2H, m), 6.81-6.79 (2H, m), 4.19 (2H, t, J = 6.5 Hz), 4.02-3.93 (2H, m), 3.19-3.14 (1H, m), 2.95 (2H, t, J = 6.5 Hz), 2.90-2.87 (1H, m), 2.36 (3H, s), 2.01-1.94 (2H, m), 1.87-1.81 (2H, m).	HR Calcd for $C_{24}H_{24}NO_5Cl$ $(M+H)^+$ 442.01416. Found 442.1413. For LR 443 $(M+H)^+$	

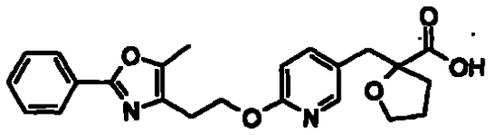
C-89		($CDCl_3$, 400 MHz) 7.81-7.75 (2H, m), 7.32-7.28 (1H, m), 7.22-7.20 1H, M0, 7.14-7.12 (2H, m), 6.81-6.78 (2H, m), 4.19 (2H, t, J = 6.5 Hz), 3.98-3.81 (2H, m), 3.17-3.10 (1H, m), 2.96 (2H, t, J = 6.5 Hz), 2.91-2.86 (1H, m), 2.38 (3H, s), 2.38 (3H, s), 2.00-1.69 (4H, m).	HR Calcd for $C_{25}H_{27}NO_5$ $(M+H)^+$ 422.1962. Found 422.1948. For LR 422 $(M+H)^+$	
C-90		($CDCl_3$, 300 MHz) 8.09-8.06 (2H, d), 7.69-7.66 (2H, d), 7.15-7.12 (2H, m), 6.82-6.79 (2H, m), 4.21 (2H, t, J = 6.5 Hz), 4.00-3.81 (2H, m), 3.18-3.14 (1H, m), 2.97 (2H, t, J = 6.5 Hz), 2.91-2.86 (1H, m), 2.39 (3H, s), 2.36-2.30 (1H, m), 2.04-1.72 (3H, m).	HR Calcd for $C_{25}H_{24}NO_5F_3$ $(M+H)^+$ 476.1680. Found 476.1661. For LR 475 $(M+H)^+$	
C-91		($CDCl_3$, 400 MHz): 7.99-7.97 (2H, m), 7.66 (1H, d, J = 9.3 Hz), 7.62-7.59 (2H, m), 7.45-7.32 (4H, m), 7.11-7.08 (2H, m), 4.31 (2H, t, J = 6.6 Hz), 3.97-3.82 (2H, m), 3.34 (1H, d, J = 13.9 Hz), 3.08-3.01 (3H, m,) 2.39-2.33 (4H, m), 2.08-2.00 (1H, m), 1.87-1.67 (2H, m)	for LR 458 $(M+H)^+$	

C-92		($CDCl_3$, 400 MHz): 7.98 (2H, d, J = 5.8 Hz), 7.68 (1H, d, J = 9.1 Hz), 7.62-7.60 (2H, m), 7.42-7.33 (4H, m), 7.14(1H, dd, J = 2.2, 8.8 Hz), 7.07 (1H, s), 4.06-3.96 (3H, m), 3.87 (1H, q, J = 7.5 Hz), 3.36 (1H, d, J = 13.9 Hz), 3.08 (1H, d, J = 13.9 Hz), 2.73 (2H, t, J = 7.1 Hz), 2.43-2.35 (1H, m), 2.27 (3H, s), 2.22-2.15 (2H, m), 2.10-2.01 (1H, m), 1.88-1.72 (2H, m)	for LR 472 $(M+H)^+$	
C-93		(MeOD, 400 MHz): 7.93-7.90 (2H, m), 7.83-7.56 (3H, m), 7.41-7.38 (3H, m), 7.31 (1H, dd, J = 2.5, 8.9 Hz), 5.01 (2H, s), 3.84-3.73 (2H, m), 3.23-3.00 (2H, m), 2.39 (3H, s), 2.23-2.16 (1H, m), 1.96-1.88 (1H, m), 1.76-1.57 (2H, m)	for LR 444 $(M+H)^+$	

Alternative Preparations of the enantiomers of 2-({6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridin-3-yl}methyl)tetrahydrofuran-2-carboxylic acid (Examples C-48a and C-48b)

Example C-48a

Enantiomer 1 of 2-({6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridin-3-yl}methyl)tetrahydrofuran-2-carboxylic acid



Lithium hydroxide monohydrate (993 mg, 21.1 mmol) was added to a solution of (4*S*)-4-benzyl-3-{[2-({6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridin-3-yl}methyl)tetrahydrofuran-2-yl]carbonyl}-1,3-oxazolidin-2-one (600 mg, 1.06 mmol) in a mixture of tetrahydrofuran:methanol:water (1:1:1, 12 mL). The mixture was stirred at 50°C for 4.5 hours, then cooled to ambient temperature and stirred for 2 days. The volatile components were removed by evaporation and the residue was diluted with water (5 mL) and extracted with 1:1 hexanes:ether. The aqueous phase was acidified to pH 5 and extracted with ethyl acetate. The organic phase was washed with brine, dried over magnesium sulfate, filtered and evaporated. The residue was purified twice by flash column chromatography (95:4:1 dichloromethane:methanol:ammonium hydroxide) to yield the title compound as a colorless oil (72 mg)

LRMS (*m/z*): 409 $(M+H)^+$.

^{1}H NMR ($CDCl_3$, 300 MHz) 7.99-7.94 (3H, m), 7.49 (1H, dd, J = 2.4, 8.6 Hz), 7.44-7.36 (3H, m), 6.63 (1H, d, J = 8.5 Hz), 4.50 (2H, t, J = 6.7 Hz), 4.00-3.93 (1H, m),

3.89-3.81 (1H, m), 3.14 (1H, d, *J* = 14.1 Hz), 2.95 (2H, t, *J* = 6.7 Hz), 2.85 (1H, d, *J* = 14.1 Hz), 2.31 (3H, s), 1.99-1.73 (4H, m).

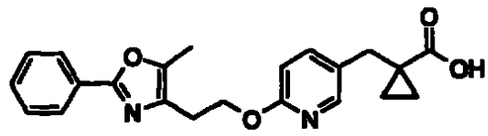
Example C-48b

Enantiomer 2 of 2-(6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridin-3-yl)methyl)tetrahydrofuran-2-carboxylic acid

Enantiomer 2 was prepared using a similar sequence of reactions to those described for enantiomer 1, except starting from (4*R*)-4-benzyl-1,3-oxazolidin-2-one.

Example C-94

1-[6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridin-3-ylmethyl]-cyclopropanecarboxylic acid



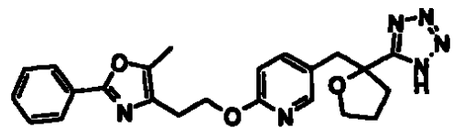
To a solution of 1-[6-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridin-3-ylmethyl]-cyclopropanecarboxylic acid *tert*-butyl ester (0.2017 g, 0.4642 mmol) in anisole (1.2 mL) was added trifluoroacetic acid (1.2 mL). The resulting solution was stirred at ambient temperature for 3 hours and then concentrated under reduced pressure. The crude residue was diluted with ethyl acetate (25 mL) and water (10 mL) and then basified to pH 5-6 by the addition of saturated aqueous sodium bicarbonate. The phases were separated and the aqueous layer extracted with ethyl acetate (3 x 25 mL). The combined organic extracts were then dried (anhydrous magnesium sulfate), filtered and concentrated *in vacuo* to afford the crude product. The pure acid (0.071 g, 40%) was obtained, by recrystallization from diethyl ether/ hexanes, as a white solid.

LRMS (*m/z*): 379 $(M+H)^+$.

^{1}H NMR (MeOD, 300 MHz): 7.89-7.83 (3H, m), 7.53 (1H, dd, *J* = 8.5, 1.9 Hz), 7.37-7.35 (3H, m), 6.60 (1H, d, *J* = 8.5 Hz), 4.39 (2H, t, *J* = 6.5 Hz), 2.87 (2H, t, *J* = 6.4 Hz), 2.73 (2H, s), 2.23 (3H, s), 1.14-1.11 (2H, m), 0.77-0.74 (2H, m).

Example C-95

2-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-5-[2-(1H-tetrazol-5-yl)-tetrahydro-furan-2-ylmethyl]-pyridine



58
59

A solution of 2-[6-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridin-3-ylmethyl]-tetrahydro-furan-2-carbonitrile (0.11 g, 0.27 mmol), sodium azide (0.04 g, 0.54 mmol) and zinc bromide (0.03 g, 0.14 mmol) in water and isopropanol (1:2, 1.24 mL) was refluxed for 23 hours. After cooling to ambient temperature, the reaction was quenched with 3N hydrochloric acid (0.14 mL) and ethyl acetate (2.8 mL), and the mixture stirred until completely homogeneous. The aqueous phase was extracted with ethyl acetate (3 x 50 mL) and the combined organic extracts washed with water (30 mL), dried (anhydrous magnesium sulfate), filtered, and concentrated *in vacuo* to give the crude product. The residue was recrystallized with diethyl ether/hexanes to afford the title compound (0.052 g, 44%) as a white solid.

Elemental Analysis: Calcd $C_{22}H_{23}N_7O_3$ C 60.96, H 5.35, N 22.62. Found: C 63.50, H 5.62, N 18.80.

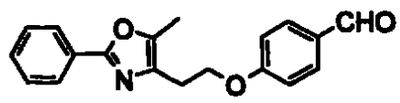
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.93 (2H, m), 7.88 (1H, s), 7.40 (3H, m), 7.11 (1H, d, *J* = 1.7 Hz), 6.49 (1H, d, *J* = 8.5 Hz), 4.42 (2H, t, *J* = 6.6 Hz), 3.88 (2H, m), 3.12 (2H, m), 2.92 (2H, t, *J* = 6.5 Hz), 2.62 (1H, m), 2.31 (3H, s), 2.23 (1H, m), 1.89 (2H, m).

LRMS (*m/z*): 433 $(M+H)^+$.

Preparations of starting materials for Examples C-1 to C-95 (Preparations c-1 to c-130)

Preparation c-1

4-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]benzaldehyde



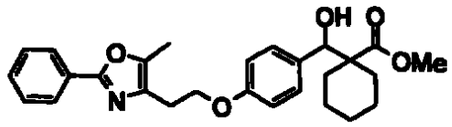
To a solution of the 4-hydroxybenzaldehyde (5.05 g, 41.4 mmol), 2-(5-methyl-2-phenyl-oxazol-4-yl)-ethan-1-ol (8.39 g, 41.4 mmol), and triphenylphosphine (10.9 g, 41.4 mmol) in anhydrous tetrahydrofuran (165 mL), under an atmosphere of nitrogen, was added diethyl azodicarboxylate (7.21 g, 41.4 mmol) dropwise. The resulting solution was stirred at ambient temperature for 6 hours, then diluted with water and extracted with ethyl acetate. The organic phase was dried (anhydrous magnesium sulfate), filtered and evaporated *in vacuo*. This residue was then purified by flash column chromatography (hexanes to ethyl acetate) to yield the title compound as a white crystalline solid (10.2 g, 80%).

LRMS (*m/z*): 308 $(M+H)^+$.

Preparation c-2

Methyl 1-(hydroxy{4-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]phenyl}methyl)

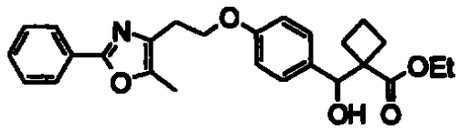
cyclohexane carboxylate



To a suspension of chromium(II) chloride (1.00 g, 8.10 mmol) and lithium iodide (0.087 g, 0.648 mmol) in tetrahydrofuran (20 mL) was added 4-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]benzaldehyde (Preparation 1) (1.00 g, 3.24 mmol) and methyl 1-bromocyclohexanoate (1.07 g, 4.85 mmol). The resulting mixture was heated at 50 °C until TLC analysis indicated the reaction was complete. The mixture was cooled to ambient temperature and saturated aqueous sodium chloride (15 mL) was added. The resulting mixture was stirred for 15 minutes, then partitioned between water and ethyl acetate. The organic phase was washed with water and dried (anhydrous magnesium sulfate), filtered and evaporated. The residue was purified by flash column chromatography (hexanes to 50% ethyl acetate/hexanes) to yield the title compound as a colorless oil (0.797 g, 55%).
LRMS (*m/z*): 450 $(M+H)^+$.

Preparation c-3

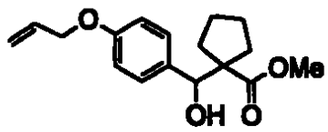
Ethyl 1-(hydroxy[4-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]phenyl]methyl)cyclobutane carboxylate



Using analogous procedures to those described for Preparation c-2, the title compound was obtained as a colorless oil.
LRMS (*m/z*): 436 $(M+H)^+$.

Preparation c-4

Methyl 1-[(4-(allyloxy)phenyl](hydroxy)methyl]cyclopentanecarboxylate



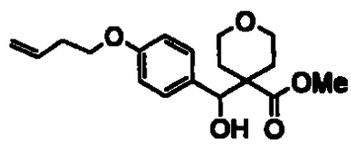
To a solution of methyl cyclopentanoate (3.84 g, 30.0 mmol), in tetrahydrofuran (30 mL) at –78 °C was added a solution of lithium diisopropylamide (15.0 mL of a 2M in tetrahydrofuran, 30.0 mmol) dropwise. The mixture was stirred for 2 hours and then 4-allyloxy benzaldehyde (2.12 g, 13.1 mmol) was added. The mixture was allowed to warm to ambient temperature and stirred for 18 hours. The mixture was diluted with water and extracted with ethyl acetate. The organic phase was

washed with saturated aqueous sodium chloride and dried (anhydrous magnesium sulfate), filtered and evaporated. The residue was purified by flash column chromatography (hexanes to 50% ethyl acetate/hexanes) to yield the title compound as a colorless oil (3.67 g, 97%).

LRMS (*m/z*): 273 $(M\text{-}OH)^+$.

Preparation c-5

Methyl 4-[[4-(but-3-enyloxy)phenyl](hydroxy)methyl]tetrahydro-2H-pyran-4-carboxylate

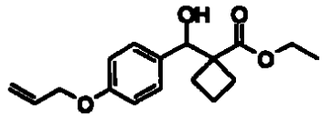


Using analogous procedures to those described for Preparation c-4, the title compound was obtained as a colorless oil.

LRMS (*m/z*): 273 $(M\text{-}OH)^+$.

Preparation c-6

Ethyl 1-[[4-(allyloxy)phenyl](hydroxy)methyl]cyclobutanecarboxylate



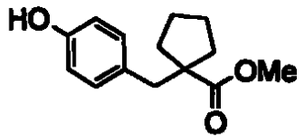
Using analogous procedures to those described for Preparation c-4, the title compound was obtained as a colorless oil.

LRMS (*m/z*): 289 $(M)^+$.

^{1}H NMR ($CDCl_3$, 300 MHz) 7.22 (2H, d, J = 8.5 Hz), 6.85 (2H, d, J = 8.7 Hz), 6.10-5.98 (1H, m), 5.39 (1H, ddd, J = 1.5, 3.2, 17.3 Hz), 5.27 (1H, ddd, J = 1.5, 2.8, 10.4 Hz), 4.85 (1H, d, J = 6.4 Hz), 4.51 (2H, dt, J = 1.5, 5.3 Hz), 4.13 (2H, dq, J = 0.9, 7.2 Hz), 3.12 (1H, d, J = 6.6 Hz), 2.84-2.78 (1H, m), 2.64-2.58 (1H, m), 2.35-2.29 (2H, m), 1.89-1.83 (1H, m), 1.72-1.66 (1H, m), 1.19 (3H, t, J = 7.0 Hz).

Preparation c-7

Methyl 1-(4-hydroxybenzyl)cyclopentanecarboxylate



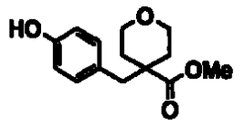
Triethylsilane (10.0 mL, 63 mmol) was added to a solution of methyl 1-[[4-(allyloxy)phenyl](hydroxy)methyl]cyclopentanecarboxylate (Preparation c-4) (3.66 g, 12.6 mmol) in dichloromethane (30 mL) and trifluoroacetic acid (30 mL) at room temperature. The resulting mixture was stirred for 1 hour then evaporated *in vacuo*

and azeotroped with toluene. The residue was dissolved in tetrahydrofuran (32 mL) and morpholine (3.62 mL, 41.6 mmol) and tetrakis(triphenylphosphine)palladium (0) (1.46 g, 1.26 mmol) was added. The resulting mixture was stirred at room temperature for 18 hours, filtered through Celite and evaporated to dryness. The residue was dissolved in ethyl acetate and washed with 1N hydrochloric acid then saturated sodium bicarbonate solution. The organic phase was dried (anhydrous magnesium sulfate), filtered and evaporated and the residue was purified by flash column chromatography (hexanes to ethyl acetate) to yield the title compound as a white crystalline solid (1.75 g, 59%).

LRMS (*m/z*): 233 $(M)^-$.

Preparation c-8

Methyl 4-(4-hydroxybenzyl)tetrahydro-2H-pyran-4-carboxylate

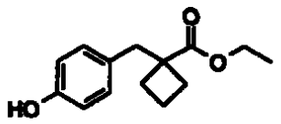


Using analogous procedures to those described for Preparation c-7, the title compound was obtained as a white crystalline solid.

LRMS (*m/z*): 249 $(M)^-$.

Preparation c-9

Ethyl 1-(4-hydroxybenzyl)cyclobutanecarboxylate



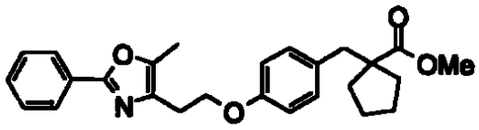
Using analogous procedures to those described for Preparation c-7, the title compound was obtained as a white crystalline solid.

LRMS (*m/z*): 234 $(M)^-$.

^{1}H NMR ($CDCl_3$, 300 MHz) 6.97 (2H, d, J = 8.5 Hz), 6.68 (2H, d, J = 8.5 Hz), 5.10 (1H, bs), 4.10 (2H, q, J = 7.2 Hz), 3.00 (2H, s), 2.44-2.35 (2H, m), 2.07-1.99 (2H, m), 1.91-1.80 (2H, m), 1.20 (3H, t, J = 7.2 Hz).

Preparation c-10

Methyl 1-[4-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]benzyl cyclopentanecarboxylate

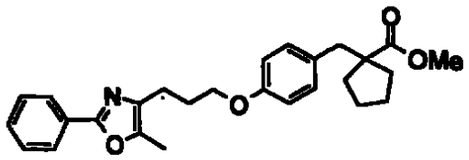


Using analogous procedures to those described for Preparation c-1-c-7, the title compound was obtained as a colorless oil.

LRMS (*m/z*): 249 $(M)^+$.

Preparation c-11

Methyl 1-[4-[3-(5-methyl-2-phenyl-1,3-oxazol-4-yl)propoxy]benzyl]cyclopentanecarboxylate

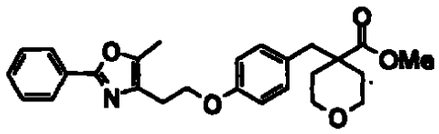


Using analogous procedures to those described for Preparation c-1-c-7, the title compound was obtained as a colorless oil.

LRMS (*m/z*): 434 $(M+H)^+$.

Preparation c-12

Methyl 4-[4-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]benzyl]tetrahydro-2*H*-pyran-4-carboxylate

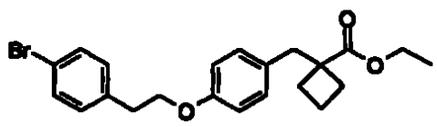


Using analogous procedures to those described for Preparation c-1-c-7, the title compound was obtained as a colorless oil.

LRMS (*m/z*): 436 $(M+H)^+$.

Preparation c-13

Ethyl 1-[4-[2-(4-bromophenyl)ethoxy]benzyl]cyclobutanecarboxylate



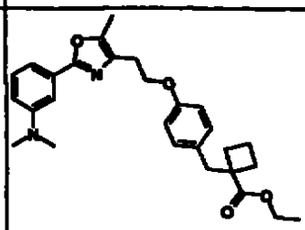
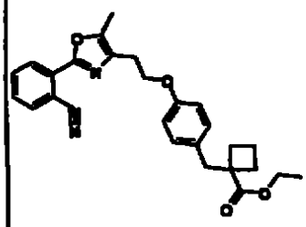
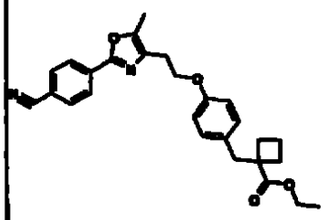
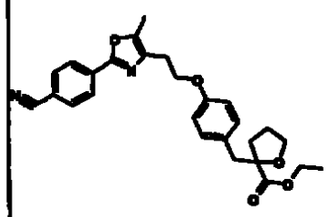
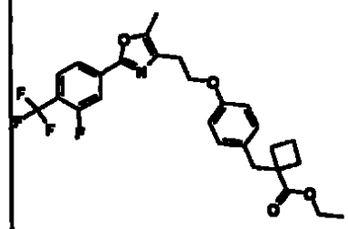
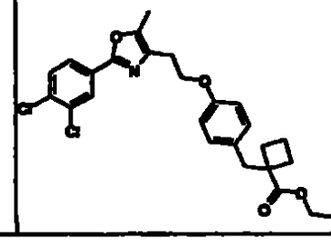
Using analogous procedures to those described for Preparation c-1-c-7, the title compound was obtained as a colorless oil.

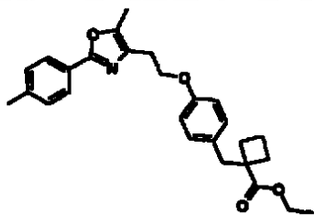
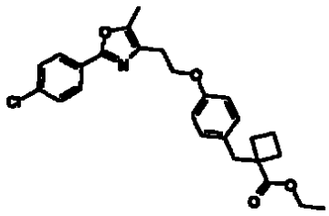
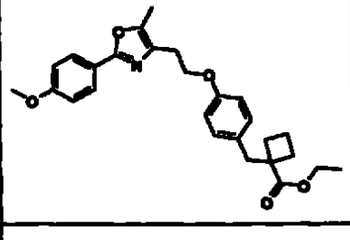
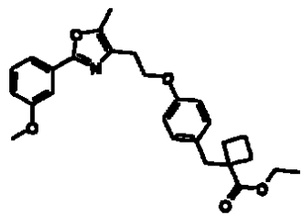
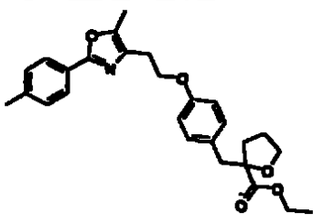
LRMS (*m/z*): 417 $(M)^+$.

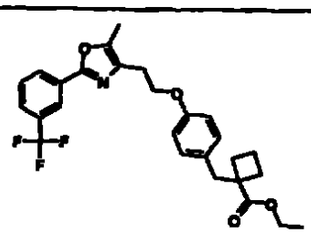
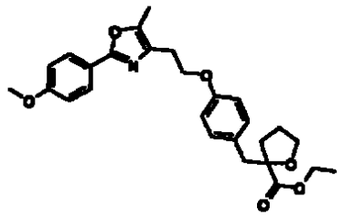
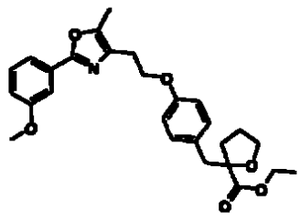
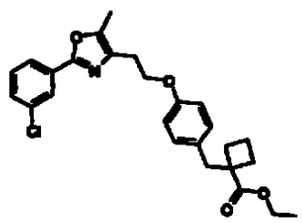
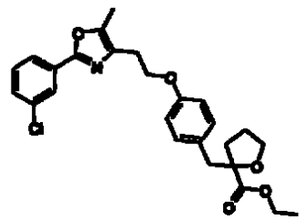
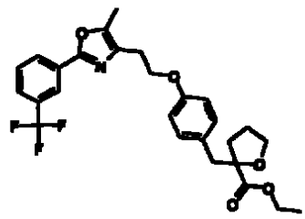
^{1}H NMR ($CDCl_3$, 300 MHz) 7.36 (2H, d, *J* = 8.3 Hz), 7.08 (2H, d, *J* = 8.3 Hz), 6.96 (2H, d, *J* = 8.7 Hz), 6.70 (2H, d, *J* = 8.7 Hz), 4.04 (2H, t, *J* = 6.8 Hz), 4.03 (2H, q, *J* = 7.2 Hz), 2.95 (2H, t, *J* = 6.8 Hz), 2.94 (2H, s), 2.37-2.27 (2H, m), 2.00-1.91 (2H, m), 1.84-1.73 (2H, m), 1.14 (3H, t, *J* = 7.2 Hz).

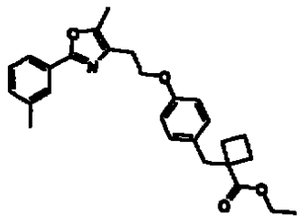
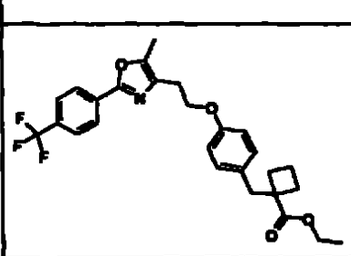
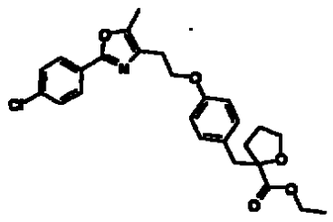
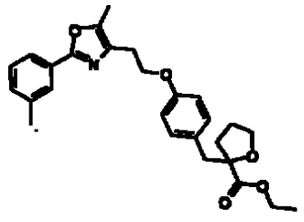
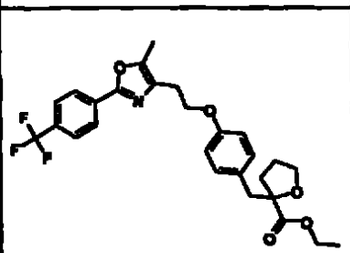
Preparations c-14 to c-35

Preparations c-14 to c-35 were prepared using analogous procedures to those used for Preparation c-1.

Prep #	Structure	^{1}H NMR	MS (*m/z*) (LR or HR)
c-14			For LR 463 $(M+H)^+$
c-15		($CDCl_3$, 300 MHz) 8.14-8.11 (1H, m), 7.78-7.75 (1H, m), 7.67-7.62 (1H, m), 7.51-7.45 (1H, m), 7.04-7.01 (2H, m), 6.80-6.78 (2H, m), 4.23 (2H, t, *J* = 6.5), 4.13-4.06 (2H, q, *J* = 7.1 Hz), 3.00 (2H, t, *J* = 3.3 Hz), 2.42 (3H, s), 2.40-2.36 (2H, m), 2.05-2.00 (2H, m), 1.87-1.84 (2H, m), 1.21 (3H, t, *J* = 7.1 Hz).	For LR 446 $(M+H)^+$
c-16		($CDCl_3$, 300 MHz) 8.07-8.04 (2H, m), 7.71-7.68 (2H, m), 7.03-7.01 (2H, m), 6.78-6.75 (2H, m), 4.19 (2H, t, *J* = 6.5 Hz), 4.13-4.06 (3H, m), 2.99 (2H, s), 2.96 (2H, t, *J* = 6.5Hz), 2.39 (3H, s), 2.38-2.34 (2H, m), 2.02-1.99 (2H, m), 1.87-1.82 (2H, m), 1.20 (3H, t, *J* = 6.9 Hz).	For LR 445 $(M+H)^+$
c-17		($CDCl_3$, 300 MHz) 8.08-8.05 (2H, m), 7.71-7.68 (2H, m), 7.16-7.13 (2H, m), 6.80-6.77 (2H, m), 5.01-4.92 (2H, m), 4.21 (2H, t, J = 6.5 Hz), 3.92-3.85 (2H, m), 3.15-3.08 (1H, m), 2.97 (2H, t, J = 6.4 Hz), 2.95-2.88 (1H, m), 2.40 (3H, s), 2.28-2.21 (1H, m), 2.04 (3H, s), 1.91-1.86 (2H, m).	For LR 461 $(M+H)^+$
c-18			For LR 506 $(M+H)^+$
c-19		($CDCl_3$, 300 MHz) 8.05-8.04 (1H, d), 7.79-7.75 (1H, m), 7.47-7.44 (1H, d), 7.03-7.00 (2H, m), 6.76-6.75 (2H, m), 4.18 (2H, t, *J* = 6.5 Hz), 4.13-4.06 (2H, q, *J* = 7.1 Hz), 3.00 (2H, s), 2.94 (2h, t, *J* = 6.5 Hz), 2.49-2.36 (2H, m), 2.35 (3H, s), 2.04-1.97 (2H, m), 1.87-1.81	For LR 489 $(M+H)^+$

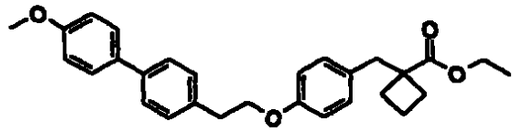
		(2H, m), 1.20 (3H, t, J = 7.1 Hz).	
c-20			For LR 435 $(M+H)^+$
c-21			For LR 455 $(M+H)^+$
c-22			For LR 450 $(M+H)^+$
c-23		($CDCl_3$, 400 MHz) 7.57-7.56 (1H, m), 7.51-7.50 (1H, m), 7.34-7.30 (1H, m), 7.03-7.01 (2H, m), 6.96-6.93 (1H, m), 6.80-6.77 (2H, m), 4.20 (2H, t, J = 6.6 Hz), 4.12-4.07 (2H, q, J = 7.0 Hz), 3.86 (3H, s), 3.00 (2H, s), 2.95 (2H, t, J = 6.5 Hz), 2.42-2.37 (2H, m), 2.35 (3H, m), 2.05-1.98 (2H, m), 1.88-1.81 (2H, m).	For LR 450 $(M+H)^+$
c-24			For LR 450 $(M+H)^+$

c-25			For LR 488 $(M+H)^+$
c-26			For LR 466 $(M+H)^+$
c-27		($CDCl_3$, 400 MHz) 7.57-7.56 (1H, m), 7.51-7.50 (1H, m), 7.34-7.30 (1H, m), 7.03-7.01 (2H, m), 6.96-6.93 (1H, m), 6.80-6.77 (2H, m), 4.20 (2H, t, J = 6.5 Hz), 4.12-4.07 (2H, q, J = 7.0 Hz), 3.86 (3H, s), 3.00 (2H, s), 2.95 (2H, t, J = 6.5 Hz), 2.42-2.37 (2H, m), 2.35 (3H, s), 2.05-1.96 (2H, m), 1.86-1.81 (2H, m) 1.20 (3H, t, J = 7.0 Hz).	For LR 450 $(M+H)^+$
c-28		($CDCl_3$, 400 MHz) 7.97 (1H, s), 7.86-7.83 (1H, s), 7.35-7.33 (2H, m), 7.03-7.01 (2H, m), 6.79-6.77 (2H, m), 4.19 (2H, t, J = 6.5 Hz), 4.12-4.07 (2H, q, J = 7.0 Hz), 3.00 (2H, s), 2.95 (2H, t, J = 6.5 Hz), 2.42-2.38 (2H, m), 2.35 (3H, s), 2.05-1.99 (2H, m), 1.91-1.82 (2H, m), 1.20 (3H, t, J = 7.0 Hz)	For LR 454 $(M+H)^+$
c-29		($CDCl_3$, 400 MHz) 7.97 (1H, s), 7.87-7.84 (1H, m), 7.36-7.35 (2H, m), 7.16-7.14 (2H, m), 6.81-6.78 (2H, m), 4.21 (2H, t, J = 6.5 Hz), 4.15-4.10 (q, J = 7.0 Hz), 3.91-3.87 (2H, m), 3.14-3.10 (1H, m), 2.96 (2H, t, J = 6.5 Hz), 2.93-2.90 (1H, m), 2.37 (3H, s), 2.26-2.12 (2H, m), 1.89-1.76 (2H, m), 1.21 (3H, t, J = 7.0 Hz).	For LR 470 $(M+H)^+$
c-30		($CDCl_3$, 400 MHz) 8.24 (1H, s), 8.16-8.14 (1H, m), 7.66-7.64 (1H, m), 7.57-7.53 (1H, m), 7.16-7.14 (2H, m), 6.81-6.79 (2H, m), 4.22 (2H, t, J = 6.5 Hz), 4.15-4.10 (2H, q, J = 7.0 Hz), 3.93-3.86 (2H, m), 3.14-3.11 (1H, m), 2.97 (2H, t, J = 6.5 Hz), 2.93-2.90 (1H, m), 2.39 (3H, s), 2.26-2.20 (2H, m), 1.91-	For LR 504 $(M+H)^+$

		1.78 (2H, m), 1.21 (3H, t, J = 7.0 Hz).	
c-31		($CDCl_3$, 300 MHz) 7.81-7.75 (2H, m), 7.32-7.27 (1H, m), 7.21-7.19 (1H, m), 7.03-7.00 (2H, m), 6.78-6.76 (2H, m), 4.19 (2H, t, J = 6.5 Hz), 4.13-4.06 (2H, q, J = 7.1 Hz), 3.00 (2H, s), 2.95 (2H, t, J = 6.5 Hz), 2.43-2.40 (2H, m), 2.37 (3H, s), 2.35 (3H, s), 2.07-1.97 (2H, m), 1.89-1.79 (2H, m), 1.19 (3H, t, J = 7.1 Hz)	For LR 434 $(M+H)^+$
c-32		($CDCl_3$, 300 MHz) 8.09-8.06 (2H, m), 7.69-7.66 (2H, m), 7.04-7.01 (2H, m), 6.80-6.77 (2H, m), 4.21 (2H, t, J = 6.5 Hz), 4.15-4.06 (2H, m), 3.00 (2H, s), 2.96 (2H, t, J = 6.5 Hz), 2.43-2.34 (5H, m), 2.01-1.97 (2H, m), 1.92-1.79 (2H, m), 1.20 (3H, t, J = 7.1 Hz)	For LR 488 $(M+H)^+$
c-33			For LR 470 $(M+H)^+$
c-34		($CDCl_3$, 300 MHz) 7.81-7.75 (1H, m), 7.33-7.27 (2H, m), 7.22-7.19 (1H, m), 7.16-7.13 (2H, m), 6.81-6.78 (2H, m), 4.20 (2H, t, J = 6.7 Hz), 4.16-4.09 (2H, q, J = 7.1 Hz), 3.94-3.82 (2H, m), 3.14-3.08 (1H, m), 2.98-2.94 (2H, t, J = 6.5 Hz), 2.94-2.88 (1H, m), 2.38 (3H, s), 2.36 (3H, s), 2.27-2.19 (1H, m), 1.92-1.74 (2H, m), 1.68-1.62 (1H, m), 1.21 (3H, t, J = 7.1 Hz).	For LR 450 $(M+H)^+$
c-35		($CDCl_3$, 300 MHz) 8.09-8.07 (2H, m), 7.69-7.66 (2H, m), 7.16-7.14 (2H, m), 6.81-6.78 (2H, m), 4.21 (2H, t, J = 6.5 Hz), 4.16-4.09 (2H, q, J = 7.1 Hz), 3.95-3.83 (2H, m), 3.15-3.10 (1H, m), 2.97 (2H, t, J = 6.5 Hz), 2.94-2.89 (1H, m), 2.39 (3H, s), 2.27-2.18 (1H, m), 1.92-1.61 (3H, m), 1.21 (3H, t, J = 7.1 Hz).	For LR 504 $(M+H)^+$

Preparation c-36

Ethyl 1-(4-[2-(4'-methoxy-1,1'-biphenyl-4-yl)ethoxy]benzyl)cyclobutanecarboxylate



To a solution of ethyl 1-(4-[2-(4-bromophenyl)ethoxy]benzyl)cyclobutanecarboxylate (Preparation c-13) (0.25 g, 0.5990 mmol), tetrakis(triphenylphosphine)palladium(0) (0.1252 g, 0.6589 mmol), benzene (1.6 mL), and 2M aqueous sodium carbonate (0.8 mL), under an atmosphere of nitrogen, was added a solution of the boronic acid (0.8640 mmol, 1.1 equiv.) in ethanol (0.4 mL). The resulting mixture was degassed and then refluxed for 16 hours followed by cooling to ambient temperature. To this was then added 30% aqueous hydrogen peroxide (0.04 mL) dropwise and the resulting solution stirred at ambient temperature for 1 hour. The solution was then extracted with ethyl acetate (3x100 mL) and the combined organic extracts washed with saturated aqueous sodium chloride (100 mL), dried (anhydrous magnesium sulfate), filtered and concentrated *in vacuo* to afford the crude product. The residue was purified by flash column chromatography (hexanes to 40% ethyl acetate/hexanes) to yield the pure product as a colorless oil.

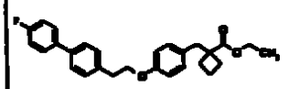
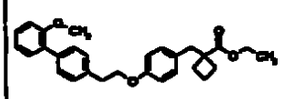
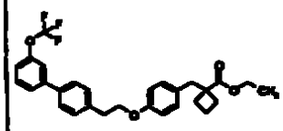
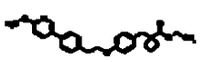
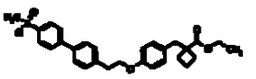
LRMS (*m/z*): 462 $(M+H_2O)^+$.

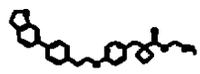
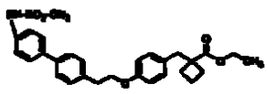
^{1}H NMR ($CDCl_3$, 300 MHz) 7.51 (2H, d, J = 5.7 Hz), 7.49 (2H, d, J = 4.7 Hz), 7.32 (2H, d, J = 8.1 Hz), 7.03 (2H, d, J = 8.5 Hz), 6.87 (2H, d, J = 8.9 Hz), 6.80 (2H, d, J = 8.5 Hz), 4.15 (1H, t, J = 7.2 Hz), 4.10 (2H, q, J = 7.2 Hz), 3.84 (3H, s), 3.10 (2H, t, J = 7.1 Hz), 3.01 (2H, s), 2.43-2.34 (2H, m), 2.07-1.98 (2H, m), 1.90-1.80 (2H, m), 1.20 (3H, t, J = 7.2 Hz).

Preparations c-37 to c-43

Preparations c-37 to c-43 were prepared using analogous procedures to those used for Preparation c-36

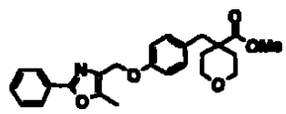
Preparation #	Structure	^{1}H NMR	MS (*m/z*) (LR or HR)

c-37		($CDCl_3$, 300 MHz) 7.46 (2H, d, J = 8.9 Hz), 7.41 (2H, d, J = 8.3 Hz), 7.27 (2H, d, J = 8.1 Hz), 7.03 (2H, t, J = 8.9 Hz), 6.97 (2H, d, J = 8.5 Hz), 6.73 (2H, d, J = 8.7 Hz), 4.09 (2H, t, J = 7.0 Hz), 4.03 (2H, q, J = 7.0 Hz), 3.03 (2H, t, J = 7.0 Hz), 2.94 (2H, s), 2.37-2.27 (2H, m), 2.00-1.91 (2H, m), 1.83-1.72 (2H, m), 1.13 (3H, t, J = 7.1 Hz).	for LR 433 $(M+H)^+$
c-38		($CDCl_3$, 300 MHz) 7.48 (2H, d, J = 8.1 Hz), 7.34-7.29 (4H, m), 7.05 (2H, d, J = 8.7 Hz), 6.99 (2H, d, J = 8.5 Hz), 6.81 (2H, d, J = 8.7 Hz), 4.18 (2H, t, J = 7.3 Hz), 4.11 (2H, q, J = 7.0 Hz), 3.81 (3H, s), 3.12 (2H, t, J = 7.3 Hz), 3.02 (2H, s), 2.44-2.35 (2H, m), 2.08-1.99 (2H, m), 1.91-1.80 (2H, m), 1.21 (3H, t, J = 7.0 Hz).	for LR 467 $(M+Na)^+$
c-39		($CDCl_3$, 300 MHz) 7.53-7.49 (3H, m), 7.44 (2H, t, J = 7.9 Hz), 7.38 (2H, t, J = 7.9 Hz), 7.09 (1H, dm, J = 8.0 Hz), 7.04 (2H, d, J = 8.5 Hz), 6.80 (2H, d, J = 8.5 Hz), 4.17 (2H, t, J = 7.0 Hz), 4.10 (2H, q, J = 7.0 Hz), 3.12 (2H, t, J = 7.0 Hz), 3.01 (2H, s), 2.44-2.35 (2H, m), 2.07-1.98 (2H, m), 1.90-1.83 (2H, m), 1.21 (3H, t, J = 7.2 Hz).	for LR 499 $(M+H)^+$
c-40		($CDCl_3$, 300 MHz) 8.36 (1H, s), 7.77 (1H, dd, J = 2.5 and 8.7 Hz), 7.46 (2H, d, J = 8.1 Hz), 7.35 (2H, d, J = 8.1 Hz), 7.03 (2H, d, J = 8.3 Hz), 6.81 (1H, d, J = 8.3 Hz), 6.79 (2H, d, J = 8.3 Hz), 4.16 (2H, t, J = 6.8 Hz), 4.09 (2H, q, J = 7.2 Hz), 3.97 (3H, s), 3.10 (2H, t, J = 7.0 Hz), 3.00 (2H, s), 2.43-2.33 (2H, m), 2.06-1.97 (2H, m), 1.89-1.79 (2H, m), 1.20 (3H, t, J = 7.1 Hz).	for LR 446 $(M+H)^+$
c-41		($CDCl_3$, 300 MHz) 7.99 (2H, d, J = 8.1 Hz), 7.75 (2H, d, J = 8.1 Hz), 7.56 (2H, d, J = 8.1 Hz), 7.40 (2H, d, J = 7.9 Hz), 7.03 (2H, d, J = 8.5 Hz), 6.79 (2H, d, J = 8.5 Hz), 4.17 (2H, t, J = 6.8 Hz), 4.09 (2H, q, J = 7.2 Hz), 3.13 (2H, t, J = 6.9 Hz), 3.06 (3H, s), 3.00 (2H, s), 2.43-2.33 (2H, m), 2.06-1.97 (2H, m), 1.90-1.79 (2H, m), 1.20 (3H, t, J = 7.2 Hz).	for LR 511 $(M+Na)^+$

c-42		($CDCl_3$, 300 MHz) 7.48 (2H, d, *J* = 8.3 Hz), 7.41 (1H, s), 7.34-7.31 (1H, m), 7.31 (2H, d, *J* = 8.3 Hz), 7.04 (2H, d, *J* = 8.7 Hz), 6.85 (1H, d, *J* = 8.5 Hz), 6.80 (2H, d, *J* = 8.5 Hz), 4.61 (2H, t, *J* = 8.7 Hz), 4.16 (2H, t, *J* = 7.2 Hz), 4.10 (2H, q, *J* = 7.2 Hz), 3.27 (2H, t, *J* = 8.7 Hz), 3.10 (2H, t, *J* = 7.0 Hz), 3.01 (2H, s), 2.44-2.36 (2H, m), 2.07-1.99 (2H, m), 1.91-1.83 (2H, m), 1.21 (3H, t, *J* = 7.2 Hz).	for LR 479 $(M+Na)^+$
c-43		($CDCl_3$, 300 MHz) 7.57 (2H, d, *J* = 8.5 Hz), 7.50 (2H, d, *J* = 8.5 Hz), 7.35 (2H, d, *J* = 8.5 Hz), 7.27 (2H, d, *J* = 8.5 Hz), 7.03 (2H, d, *J* = 8.7 Hz), 6.79 (2H, d, *J* = 8.7 Hz), 6.37 (1H, bs), 4.16 (2H, t, *J* = 7.0 Hz), 4.09 (2H, q, *J* = 7.0 Hz), 3.11 (2H, d, *J* = 7.0 Hz), 3.04 (3H, s), 3.00 (2H, s), 2.43-2.33 (2H, m), 2.06-1.97 (2H, m), 1.89-1.79 (2H, m), 1.20 (3H, t, *J* = 7.2 Hz).	for LR 508 $(M)^+$

Preparation c-44

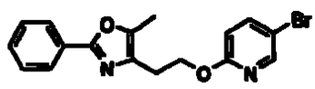
Methyl 4-[4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyl]tetrahydro-2H-pyran-4-carboxylate



A solution of methyl 4-(4-hydroxybenzyl)tetrahydro-2H-pyran-4-carboxylate (Preparation c-8) (0.500 g, 2.0 mmol), cesium carbonate (1.96 g, 6.0 mmol) and chloride (0.458 g, 2.2 mmol) in acetonitrile was heated at 140 °C in a microwave synthesizer for 10 minutes. The mixture was cooled, filtered and the filtrate evaporated. The residue purified by flash column chromatography (hexanes to ethyl acetate) to yield the title compound as a white crystalline solid (0.827 g, 98%). LRMS (*m/z*): 422 $(M+H)^+$.

Preparation c-45

5-Bromo-2-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridine



To a solution of 2,5-dibromo-pyridine (5 g, 21.1080 mmol) and 2-(5-methyl-2-phenyl-oxazol-4-yl)-ethanol (5.1472 g, 25.3271 mmol) in anhydrous tetrahydrofuran

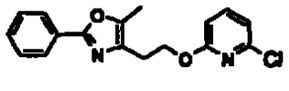
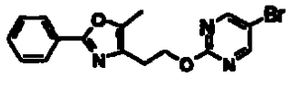
(85 mL), under an atmosphere of nitrogen, was added potassium *tert*-butoxide (2.8422 g, 25.3271 mmol). The resulting mixture was heated at reflux for 16 hours and then allowed to cool to ambient temperature. The mixture was evaporate to about 20 mL and partitioned between saturated aqueous ammonium chloride (50 mL) and ethyl acetate (50 mL). The layers were separated and the aqueous layer extracted with ethyl acetate (2x50 mL). The combined organic extracts were then washed with water (2x50 mL), saturated aqueous sodium chloride (50 mL), dried (anhydrous magnesium sulfate), filtered and concentrated *in vacuo* to afford the crude product. The residue was purified by flash column chromatography (hexanes to 20% ethyl acetate/hexanes) to yield a white crystalline solid (6.3 g, 83%).

LRMS (*m/z*): 359 $(M)^+$.

^{1}H NMR ($CDCl_3$, 400 MHz) 8.17 (1H, d, *J* = 2.0 Hz), 7.98 (2H, dd, *J* = 2.0, 8.1 Hz), 7.61 (1H, dd, *J* = 2.7, 8.7 Hz), 7.43-7.38 (3H, m), 6.62 (1H, d, *J* = 8.6 Hz), 4.52 (2H, t, *J* = 6.8 Hz), 2.96 (2H, t, *J* = 6.8 Hz), 2.32 (3H, s).

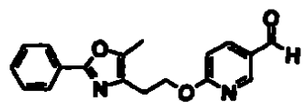
Preparations c-46 to c-47

Preparations c-46 to c-47 were prepared by general procedure for Preparation c-45.

Prep #	Structure	^{1}H NMR	MS (*m/z*) (LR or HR)
c-46		($CDCl_3$, 400 MHz): 7.97 (2H, dd, *J* = 8.0, 7.6 Hz), 7.49 (1H, dd, *J* = 8.1, 7.6 Hz), 7.43-7.38 (3H, m), 6.87 (1H, d, *J* = 7.6 Hz), 6.62 (1H, d, *J* = 8.1 Hz), 4.55 (2H, t, *J* = 7.0 Hz), 2.97 (2H, t, *J* = 7.0 Hz), 2.34 (3H, s)	for LR 315 $(M+H)^+$
c-47		($CDCl_3$, 300 MHz): 8.51 (2H, s), 7.97-7.94 (2H, m), 7.45-7.38 (3H, m), 4.61 (2H, t, *J* = 6.9 Hz), 3.01 (2H, t, *J* = 6.9 Hz), 2.35 (3H, s)	for LR 361 $(M+H)^+$

Preparation c-48

6-[2-(5-Methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]nicotinaldehyde



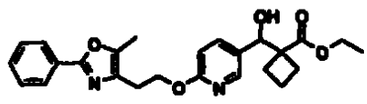
To a solution of butyllithium (27.4 mL of a 1.6M solution in hexanes, 43.8199 mmol) in anhydrous tetrahydrofuran (200 mL), under an atmosphere of nitrogen, was added a solution of 5-bromo-2-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridine (Preparation c-45) (14.31 g, 39.8363 mmol) in anhydrous tetrahydrofuran (170 mL) and anhydrous diethyl ether (170 mL) over a period of 45 minutes. To this solution was then added anhydrous *N,N*-dimethylformamide (5.7 mL) dropwise and the mixture stirred at 0 °C for 1 hour. The reaction was quenched by addition of saturated aqueous ammonium chloride (250 mL) and then ethyl acetate (250 mL). The resulting layers were separated and the aqueous layer extracted with ethyl acetate (2x250 mL). The combined organic extracts were washed with water (2x250 mL), saturated aqueous sodium chloride (250 mL), dried (anhydrous magnesium sulfate), filtered and concentrated *in vacuo* to afford the crude product. The residue was purified by flash column chromatography (hexanes to 50% ethyl acetate/hexanes) to yield a pale yellow crystalline solid (7.17 g, 58%).

LRMS (*m/z*): 309 $(M+H)^+$.

^{1}H NMR ($CDCl_3$, 300 MHz) 9.93 (1H, s), 8.61 (1H, d, *J* = 2.3 Hz), 8.04 (1H, dd, *J* = 2.5, 8.7 Hz), 7.98-7.95 (2H, m), 7.43-7.39 (3H, m), 6.81 (1H, d, *J* = 8.7 Hz), 4.68 (2H, t, *J* = 6.8 Hz), 3.00 (2H, t, *J* = 6.8 Hz), 2.34 (3H, s).

Preparation c-49

Ethyl 1-(hydroxy{6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridin-3-yl}methyl)cyclobutanecarboxylate



To a solution of 6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]nicotinaldehyde (Preparation c-48) (0.85 g, 2.1081 mmol), chromium (II) chloride (1 g, 8.1367 mmol), and lithium iodide (0.0784 g, 0.5859 mmol) in anhydrous tetrahdrofuran (15 mL), under an atmosphere of nitrogen, was added a solution of 1-bromo-cyclobutanecarboxylic acid ethyl ester (0.79 mL, 4.8821 mmol) in anhydrous

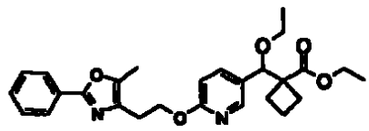
tetrahydrofuran (5 mL) dropwise. The resulting mixture was stirred at 50 °C for 3 hours and allowed to cool to ambient temperature. The solution was then quenched by addition of water (50 mL) and the organic layer separated, which was further washed with water (2x50 mL), saturated aqueous sodium chloride (50 mL), dried (anhydrous magnesium sulfate), filtered and concentrated *in vacuo* to afford the crude product. The residue was purified by flash column chromatography (50% ethyl acetate/hexanes to ethyl acetate) to yield a yellow oil (0.3422 g, 37%).

LRMS (*m/z*): 437 $(M+H)^+$.

^{1}H NMR ($CDCl_3$, 400 MHz) 8.05 (1H, d, *J* = 2.3 Hz), 7.98-7.95 (2H, m), 7.56 (1H, dd, *J* = 2.5, 8.7 Hz), 7.44-7.37 (3H, m), 6.67 (1H, d, *J* = 8.7 Hz), 4.85 (1H, d, *J* = 6.6 Hz), 4.54 (2H, t, *J* = 6.6 Hz), 4.18-4.07 (2H, m), 3.31 (1H, bs), 2.96 (2H, t, *J* = 6.7 Hz), 2.46-2.30 (2H, m), 2.32 (3H, s), 2.21-2.12 (1H, m), 1.97-1.85 (1H, m), 1.79-1.65 (2H, m), 1.21 (3H, t, *J* = 7.2 Hz).

Preparation c-50

1-(Ethoxy-{6-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridin-3-yl}-methyl)-cyclobutanecarboxylic acid ethyl ester



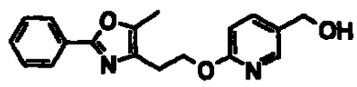
To a solution of 1-(hydroxy-{6-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridin-3-yl}-methyl)-cyclobutanecarboxylic acid ethyl ester (0.1711 g, 0.3920 mmol) in dry acetonitrile (2 mL) was added silver(I) oxide (1.8188 g, 7.8396 mmol) and iodoethane (0.64 mL, 7.8396 mmol). The resulting mixture was stirred for 5 days and concentrated under reduced pressure to afford the crude product and recovered remaining starting material. The residue was purified by flash column chromatography (hexanes to ethyl acetate) to yield the pure ester (0.0474 g, 26%) as a colorless oil.

LRMS (*m/z*): 465 $(M+H)^+$.

^{1}H NMR ($CDCl_3$, 400 MHz): 8.05 (1H, d, *J* = 2.3 Hz), 7.98-7.95 (2H, m), 7.56 (1H, dd, *J* = 2.5, 8.7 Hz), 7.44-7.37 (3H, m), 6.67 (1H, d, *J* = 8.7 Hz), 4.65 (1H, m), 4.54 (2H, t, *J* = 6.6 Hz), 4.18-4.07 (2H, m), 4.06 (2H, q, *J* = 7.1 Hz), 2.96 (2H, t, *J* = 6.7 Hz), 2.46-2.30 (2H, m), 2.32 (3H, s), 2.21-2.12 (1H, m), 1.97-1.85 (1H, m), 1.79-1.65 (2H, m), 1.42 (3H, t, *J* = 7.1 Hz), 1.21 (3H, t, *J* = 7.2 Hz).

Preparation c-51

6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridin-3-yl)methanol



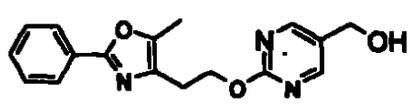
Sodium borohydride (0.480 g, 12.7 mmol) was added portionwise to a solution of 6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]nicotinaldehyde (Preparation c-48) (1.30 g, 4.22 mmol) in methanol (40 mL) at ambient temperature. The mixture was stirred for 30 minutes then evaporated. The residue was partitioned between saturated aqueous ammonium chloride and ethyl acetate. The organic phase was washed with saturated aqueous sodium chloride and dried (anhydrous magnesium sulfate), filtered and evaporated to give the title compound as a white crystalline solid (1.24 g, 100%).

LRMS (*m/z*): 311 $(M+H)^+$.

^{1}H NMR ($CDCl_3$, 300 MHz) 8.11 (1H, d, *J* = 2.6 Hz), 8.00-7.95 (2H, m), 7.60 (1H, dd, *J* = 2.5, 8.5 Hz), 7.45-7.38 (3H, m), 6.72 (1H, d, *J* = 8.5 Hz), 4.61 (2H, bs), 4.56 (2H, t, *J* = 6.8 Hz), 2.98 (2H, t, *J* = 6.8 Hz), 2.33 (3H, s).

Preparation c-52

[2-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyrimidin-5-yl]-methanol



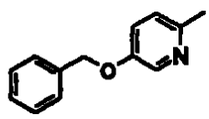
A solution of 5-bromo-2-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyrimidine (1.0 g, 2.7765 mmol), *tert*-butyl-dimethyl-tributylstannanylmethoxy-silane (1.8 g, 4.1648 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.3209 g, 0.2777 mmol) in 1,4-dioxane (2.8 mL) was heated (by microwave irradiation) at 150 °C for 2 hours. The resulting solution was allowed to cool to ambient temperature and saturated aqueous potassium fluoride (10 mL) was added followed by stirring for 30 minutes. This mixture was then extracted with ethyl acetate (3 x 25 mL) and the combined organic extracts dried (anhydrous magnesium sulfate), filtered and concentrated *in vacuo* to afford the crude product as a yellow oil.

To a solution of the crude residue in dry tetrahydrofuran (24 mL) was added tetrabutylammonium fluoride (3.1 mL of a 1.0M solution in tetrahydrofuran). The resulting mixture was stirred at ambient temperature for 16 hours and concentrated under reduced pressure. The residue was purified by flash column

chromatography (50% ethyl acetate/hexanes to 10% methanol/ethyl acetate) to yield the pure alcohol (0.6137 g, 71% for 2 steps) as a white solid.
LRMS (*m/z*): 312 $(M+H)^+$

Preparation c-53

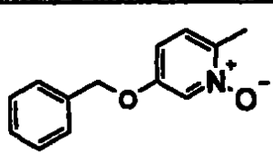
5-Benzyloxy-2-methyl-pyridine



To a solution of 5-hydroxy-2-methylpyridine (20 g, 183.2677 mmol) and sodium hydroxide (8.0638 g, 201.5944 mmol) in acetone (400 mL) and water (120 mL) was added benzyl bromide (24 mL, 201.5944 mmol). The resulting mixture was refluxed for 16 hours and allowed to cool to ambient temperature. The acetone was removed *in vacuo* and the mixture extracted with ethyl acetate (3 x 150 mL). The combined organic extracts were washed with saturated aqueous sodium chloride (200 mL), dried (anhydrous magnesium sulfate), filtered and concentrated *in vacuo* to afford the pure product (31.35 g, 86%) as an orange oil
LRMS (*m/z*): 200 $(M+H)^+$.
^{1}H NMR ($CDCl_3$, 300 MHz): 8.25 (1H, d, J = 2.8 Hz), 7.43-7.31 (5H, m), 7.15 (1H, dd, J = 8.5, 2.8 Hz), 7.04 (1H, d, J = 8.5 Hz), 5.06 (2H, s), 2.47 (3H, s).

Preparation c-54

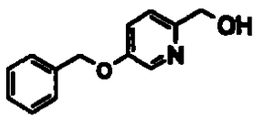
5-Benzyloxy-2-methyl-pyridine 1-oxide



To a solution of 5-benzyloxy-2-methyl-pyridine (31.35 g, 157.34 mmol) in dry chloroform (800 mL), at ambient temperature, was added 3-chloroperoxybenzoic acid (77% max.) (38.7888 g, 173.074 mmol). The resulting mixture was stirred for 2 hours and then quenched with a solution of sodium thiosulfate (36.0805 g, 286.5 mmol) in water (500 mL) and stirred for 15 minutes. The phases were separated and the organic layer washed with water (500 mL), saturated sodium chloride (500 mL), dried (anhydrous magnesium sulfate), filtered and concentrated *in vacuo* to afford the crude product. The residue was recrystallized from acetone/hexanes to yield the pure product (33.1597 g, 97%) as a white solid.
LRMS (*m/z*): 216 $(M+H)^+$.
^{1}H NMR ($CDCl_3$, 300 MHz): 8.10-8.09 (1H, bm), 7.38-7.34 (5H, m), 7.10 (1H, d, J = 8.7 Hz), 6.87 (1H, dd, J = 8.7, 2.3 Hz), 5.04 (2H, s), 2.43 (3H, s).

Preparation c-55

(5-Benzyloxy-pyridin-2-yl)-methanol



A solution of 5-benzyloxy-2-methyl-pyridine 1-oxide (0.82 g, 4.2741 mmol) in acetic anhydride (8.5 mL) was heated at 100 °C for 30 minutes. After cooling to ambient temperature, the reaction mixture was poured into ethyl acetate (50 mL), washed with saturated aqueous sodium bicarbonate (50 mL), saturated aqueous sodium chloride (50 mL), dried (anhydrous magnesium sulfate), filtered, and concentrated *in vacuo* to afford the crude acetate.

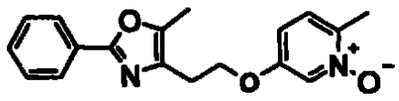
To the crude residue in methanol (45 mL) was added potassium carbonate (2.1784 g, 15.7719 mmol) and the solution allowed to stir at ambient temperature for 16 hours. The reaction mixture was poured into water (50 mL) and the organic removed under reduced pressure. The resulting residue was extracted with ethyl acetate (3 x 50 mL) and the combined organic extracts dried (anhydrous magnesium sulfate), filtered, and concentrated *in vacuo* to afford the crude product. The residue was purified by flash column chromatography (hexanes to 20% methanol/ethyl acetate) to yield the pure alcohol (0.5719 g, 62% for two steps) as a white solid.

LRMS (*m/z*): 216 $(M+H)^+$.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.31 (1H, d, *J* = 2.8 Hz), 7.44-7.31 (5H, m), 7.27 (1H, dd, *J* = 8.7, 2.8 Hz), 7.17 (1H, d, *J* = 8.5 Hz), 5.11 (2H, s), 4.69 (2H, s).

Preparation c-56

2-Methyl-5-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridine 1-oxide



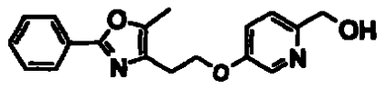
To a solution of 2-methyl-5-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridine (6.7973 g, 23.0917 mmol) in dry chloroform (140 mL), at ambient temperature, was added 3-chloroperoxybenzoic acid (77% max.) (7.7629 g, 34.6376 mmol). The resulting mixture was stirred for 2 hours and then quenched with a solution of sodium thiosulfate (4.3621 g, 34.6376 mmol) in water (25 mL) and stirred for 15 minutes. The phases were separated and the organic layer washed with water (50 mL), saturated sodium chloride (50 mL), dried (anhydrous magnesium sulfate), filtered and concentrated *in vacuo* to afford the crude product. This pale yellow oil (7.0689 g, 98%) was used without further purification.

LRMS (*m/z*): 311 $(M+H)^+$.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.06 (1H, d, *J* = 2.3 Hz), 7.96-7.93 (2H, m), 7.41-7.39 (3H, m), 7.10 (1H, d, *J* = 8.9 Hz), 6.85 (1H, dd, *J* = 8.8, 2.4 Hz), 4.23 (2H, t, *J* = 6.6 Hz), 2.95 (2H, t, *J* = 6.6 Hz), 2.43 (3H, s), 2.35 (3H, s).

Preparation c-57

{5-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridin-2-yl}-methanol



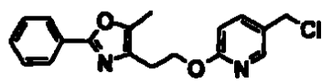
A solution of 2-methyl-5-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridine 1-oxide (3.5979 g, 11.5181 mmol) in acetic anhydride (17.5 mL) was heated at 100 °C for 30 minutes. After cooling to ambient temperature, the reaction mixture was poured into ethyl acetate (150 mL), washed with saturated aqueous sodium bicarbonate (150 mL), saturated aqueous sodium chloride (150 mL), dried (anhydrous magnesium sulfate), filtered, and concentrated *in vacuo* to afford the crude acetate. To the crude residue in methanol (120 mL) was added potassium carbonate (5.8705 g, 42.617 mmol) and the solution allowed to stir at ambient temperature for 16 hours. The reaction mixture was poured into water (150 mL) and the organic removed under reduced preasure. The resulting residue was extracted with ethyl acetate (3 x 150 mL) and the combined organic extracts dried (anhydrous magnesium sulfate), filtered, and concentrated *in vacuo* to afford the crude product. The residue was purified by flash column chromatography (ethyl acetate to 10% methanol/ethyl acetate) to yield the pure alcohol (1.52 g, 43% for two steps) as a pale yellow low melting solid.

LRMS (*m/z*): 311 $(M+H)^+$.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.22 (1H, d, *J* = 2.5 Hz), 7.97-7.94 (2H, m), 7.42-7.38 (3H, m), 7.20 (1H, dd, *J* = 8.5, 2.6 Hz), 7.15 (1H, d, *J* = 8.7 Hz), 4.67 (2H, s), 4.28 (2H, t, *J* = 6.7 Hz), 2.98 (2H, t, *J* = 6.7 Hz), 2.37 (3H, s).

Preparation c-58

5-(chloromethyl)-2-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridine

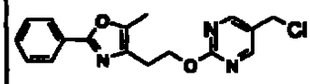
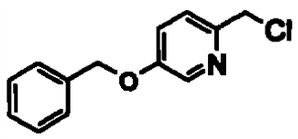
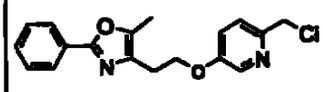
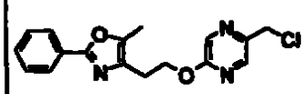
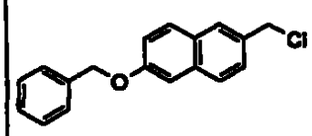


Oxalyl chloride (0.30 mL, 3.44 mmol) was added to a solution of {6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridin-3-yl}methanol (Preparation 26) (0.97 g, 3.13 mmol) in dichloromethane (30 mL) and *N,N*-dimethyl formamide (3 mL) at 0 °C. The mixture was warmed to ambient temperature and stirred for 1 hour then evaporated. The residue was partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. The organic phase was washed with saturated

aqueous sodium chloride and dried (anhydrous magnesium sulfate), filtered and evaporated to give the title compound as a white crystalline solid (1.01 g, 100%).
LRMS (*m/z*): 329 $(M+H)^+$.
^{1}H NMR ($CDCl_3$, 300 MHz) 8.12 (1H, d, *J* = 2.5 Hz), 7.98-7.95 (2H, m), 7.60 (1H, dd, *J* = 2.5, 8.5 Hz), 7.45-7.37 (3H, m), 6.72 (1H, d, *J* = 8.5 Hz), 4.57 (2H, t, *J* = 6.8 Hz), 4.53 (2H, s), 2.97 (2H, t, *J* = 6.8 Hz), 2.33 (3H, s).

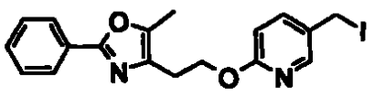
Preparations c-59 to c-63

Preparations c-59 to c-63 were prepared by general procedure for Preparation c-58

Prep #	Structure	^{1}H NMR	MS (*m/z*) (LR or HR)
c-59			for LR 330 $(M+H)^+$
c-60			for LR 234 $(M+H)^+$
c-61			for LR 329 $(M+H)^+$
c-62		($CDCl_3$, 300 MHz): 8.16 (2H, s), 7.97 (2H, d, J = 7.7 Hz), 7.40 (3H, s), 4.61 (4H, m), 2.99 (2H, t, J = 6.7 Hz), 2.35 (3H, s)	for LR 330 $(M+H)^+$
c-63		($CDCl_3$, 400 MHz): 7.75-7.72 (3H, m), 7.50-7.33 (6H, m), 7.24-7.22 (2H, m), 5.18 (2H, s), 4.74 (2H, s)	for LR 282 $(M+H)^+$

Preparation c-64

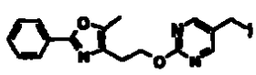
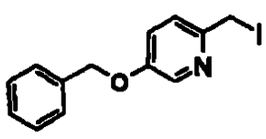
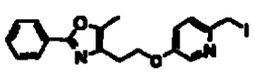
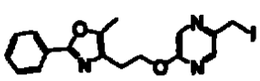
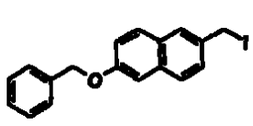
5-(Iodomethyl)-2-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridine



Sodium iodide (0.750 g) was added to a solution of 5-(chloromethyl)-2-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridine (Preparation 27) (0.690 g, 2.10 mmol) in acetone (5 mL) and the mixture was heated at reflux for 30 minutes, cooled and evaporated. The residue was suspended in ethyl acetate and filtered through a pad of silica gel. The filtrate was evaporated to give the title compound as a yellow crystalline solid that was used directly in subsequent reactions.
LRMS (*m/z*): 421 $(M+H)^+$.

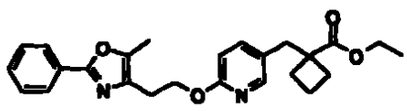
Preparations c-65 to c-69

Preparations c-65 to c-69 were prepared by general procedure for Preparation c-64

Prep #	Structure	^{1}H NMR	MS (*m/z*) (LR or HR)
c-65			for LR 422 $(M+H)^+$
c-66			for LR 328 $(M+H)^+$
c-67			for LR 421 $(M+H)^+$
c-68			for LR 422 $(M+H)^+$
c-69		($CDCl_3$, 400 MHz): 7.76-7.66 (3H, m), 7.49-7.32 (6H, m), 7.24-7.18 (2H, m), 5.18 (2H, s), 4.63 (2H, s)	for LR 375 $(M+H)^+$

Preparation c-70

Ethyl 1-({6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridin-3-yl}methyl)cyclobutane carboxylate



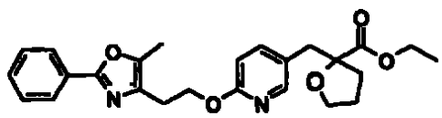
Sodium (bis)trimethylsilyl amide (3.0 mL of a 1M solution in tetrahydrofuran, 3.0 mmol) was added dropwise to a solution of ethyl cyclobutanoate (0.41 mL, 3.0 mmol) in anhydrous tetrahydrofuran (5 mL) at –60 °C. The mixture was stirred for 1 hour and then a solution of 5-(iodomethyl)-2-[2-(5-methyl-2-phenyl-1,3-oxazol-4-

yl)ethoxy]pyridine (Preparation 28) (0.271 g, 0.64 mmol) in anhydrous tetrahydrofuran (4 mL) was added dropwise. The resulting mixture was stirred at –60 °C for 1 hour then quenched with saturated aqueous ammonium chloride and warmed to ambient temperature. The mixture was extracted with ethyl acetate and the organic phase dried (anhydrous magnesium sulfate), filtered and evaporated to afford a 1:1 mixture of the title compound and dimer (0.160 g) which was used directly in the subsequent step.

LRMS (*m/z*): 421 $(M+H)^+$.

Preparation c-71

ethyl 2-({6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridin-3-yl}methyl)tetrahydrofuran-2-carboxylate



Sodium (bis)trimethylsilyl amide (3.18 mL of 1M solution in tetrahydrofuran, 3.18 mmol) was added dropwise to a solution of ethyl 2-tetrahydrofuranoate (0.458 g, 3.18 mmol) in anhydrous tetrahydrofuran (4 mL) at –50 °C. The mixture was stirred for 45 minutes and then a solution of 5-(iodomethyl)-2-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridine (Preparation 28) (0.267 g, 0.64 mmol) in anhydrous tetrahydrofuran (2 mL) was added dropwise. The resulting mixture was stirred at –50 °C for 1.5 hours then quenched with saturated aqueous ammonium chloride and warmed to ambient temperature. The mixture was extracted with ethyl acetate and the organic phase dried (anhydrous magnesium sulfate), filtered and evaporated. The residue was purified by flash column chromatography (25% to 35% ethyl acetate/hexanes) to yield the title compound as a colorless oil (0.250 g, 90%).

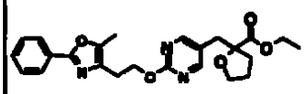
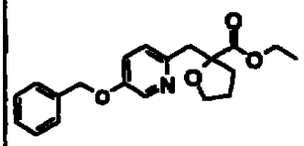
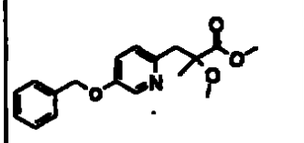
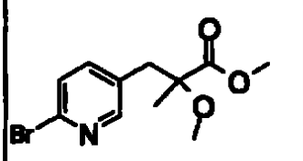
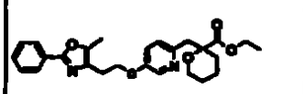
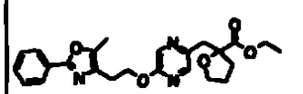
LRMS (*m/z*): 437 $(M+H)^+$.

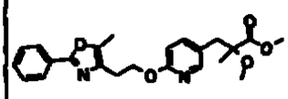
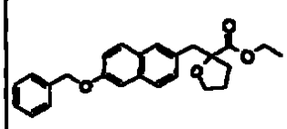
^{1}H NMR ($CDCl_3$, 300 MHz) 7.95 (3H, m), 7.51 (1H, dd, J = 2.5, 8.5 Hz), 7.43-7.36 (3H, m), 6.61 (1H, d, J = 8.5 Hz), 4.51 (2H, t, J = 6.8 Hz), 4.29-4.18 (1H, m), 413 (2H, q, J = 7.2 Hz), 3.95-3.82 (2H, m), 3.10 (1H, d, J = 14.1 Hz), 2.95 (2H, t, J = 6.8 Hz), 2.86 (1H, d, J = 14.1 Hz), 2.31 (3H, s), 2.26-2.20 (1H, m), 1.92-1.77 (2H, m), 1.70-1.61 (1H, m), 1.21 (3H, t, J = 7.2 Hz).

Preparations c-72 to c-79

Preparations c-72 to c-79 were prepared by general procedure for Preparation c-71.

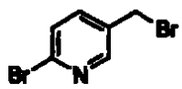
Prep #	Structure	^{1}H NMR	MS (*m/z*) (LR or

			HR)
c-72		($CDCl_3$, 300 MHz): 8.38 (2H, s), 7.97-7.94 (2H, m), 7.44-7.38 (3H, m), 4.59 (2H, t, J = 7.0 Hz), 4.15 (2H, q, J = 7.0 Hz), 3.99-3.86 (2H, m), 3.13 (1H, d, J = 14.3 Hz), 3.00 (1H, t, J = 6.9 Hz), 2.84 (1H, d, J = 14.3 Hz), 2.35 (3H, s), 2.26-2.20 (1H, m), 1.91-1.63 (4H, m), 1.23 (3H, t, J = 7.0 Hz)	for LR 438 $(M+H)^+$
c-73		($CDCl_3$, 300 MHz): 8.27 (1H, d, J = 2.3 Hz), 7.42-7.32 (5H, m), 7.20-7.13 (2H, m), 5.06 (2H, s), 4.13 (2H, q, J = 13.9 Hz), 3.33 (1H, d, J = 13.9 Hz), 3.14 (1H, d, J = 13.9 Hz), 2.64-2.55 (1H, m), 2.27-2.20 (1H, m), 1.86-1.63 (4H, m), 1.24 (3H, t, J = 13.9 Hz)	for LR 342 $(M+H)^+$
c-74		($CDCl_3$, 300 MHz): 8.27 (1H, d, J = 2.6 Hz), 7.42-7.29 (5H, m), 7.16 (1H, dd, J = 8.7, 2.8 Hz), 7.14-7.08 (1H, m), 5.06 (2H, s), 3.71 (3H, s), 3.30 (3H, s), 3.16 (2H, s), 1.40 (3H, s)	for LR 316 $(M+H)^+$
c-75		($CDCl_3$, 400 MHz): 8.14 (1H, d, J = 2.3 Hz), 7.41 (1H, dd, J = 8.3, 2.5 Hz), 7.36 (1H, dd, J = 8.3, 0.8 Hz), 3.69 (3H, s), 3.27 (3H, s), 2.99 (1H, d, J = 13.9 Hz), 2.87 (1H, d, J = 13.9 Hz), 1.33 (3H, s)	for LR 289 $(M+H)^+$
c-76		($CDCl_3$, 400 MHz): 8.17 (1H, d, J = 2.3 Hz), 7.96 (2H, dd, J = 7.7, 1.9 Hz), 7.43-7.38 (3H, m), 7.12 (1H, d, J = 8.1 Hz), 7.09 (1H, dd, J = 8.6, 2.6 Hz), 4.24 (2H, t, J = 6.7 Hz), 4.15 (2H, q, J = 7.2 Hz), 3.88-3.84 (1H, m), 3.64 (1H, dt, J = 11.6, 3.3 Hz), 3.07 (2H, s), 2.96 (2H, t, J = 6.6 Hz), 2.36 (3H, s), 2.22-2.18 (1H, m), 1.52-1.36 (5H, m), 1.20 (3H, t, J = 7.1 Hz)	for LR 451 $(M+H)^+$
c-77		($CDCl_3$, 300 MHz); 8.09 (1H, s), 7.91-8.01 (3H, m), 7.34-7.45 (3H, m), 4.48–4.64 (2H, m), 3.84–4.24 (2H, m), 3.22 (1H, d, J = 15.0 Hz), 3.11 (1H, d, J = 15.0 Hz), 2.91-3.03 (1H, m), 2.31–2.35 (1H, m), 1.65-2.30 (2H, m), 1.24 (3H, t, J = 6.6 Hz)	for LR 438 $(M+H)^+$

c-78		($CDCl_3$, 300 MHz): 7.98 (1H, m), 7.92 (2H, d, J = 2.1 Hz), 7.41 (4H, m), 6.63 (1H, d, J = 8.5 Hz), 4.52 (2H, t, J = 6.6 Hz), 3.70 (3H, s), 3.30 (3H, m), 2.93 (4H, m), 2.33 (3H, s), 1.33 (3H, s)	for LR 411 $(M+H)^+$
c-79		($CDCl_3$, 400 MHz): 7.69 (1H, d, J = 9.3 Hz), 7.64-7.62 (2H, m), 7.49-7.48 (2H, m), 7.42-7.32 (4H, m), 7.21-7.18 (2H, m), 5.17 (2H, s), 4.24-4.18 (2H, m), 3.96-3.86 (2H, m), 3.33 (1H, d, J = 13.8 Hz), 3.13 (1H, d, J = 13.8 Hz), 2.32-2.20 (1H, m), 2.03-1.89 (3H, m), 1.19 (3H, t, J = 7.1 Hz)	for LR 391 $(M+H)^+$

Preparation c-80

2-Bromo-5-(bromomethyl)pyridine



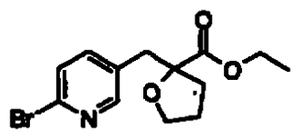
Phosphorous tribromide (100 mmol, 27.1 g, 2.0 eq.) was added carefully to 2-chloro-5-hydroxymethyl pyridine (50.0 mmol, 7.18 g, 1.0 eq.). The pyridine clumped together and the mixture was heated to 160 degrees C. Within 5 minutes of stirring at > 150 degrees C the mixture was seen to go very dark in color with gas evolution. The mixture was stirred at this same temperature for approximately 2.5 hours at which point it was cooled to room temperature. The mixture was cooled further to 0 degrees C whereupon saturated sodium bicarbonate was added very cautiously (highly exothermic!). As foaming became less vigorous, ice was added to the mixture until foaming subsided. Solid sodium bicarbonate was then carefully added to achieve a pH of ~ 8-9. The mixture was extracted with ethyl acetate and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. Concentrated in vacuo to afford a dark solid. This material was dissolved in a minimal amount of DCM and purified using a Biotage Sp4 65i over a gradient of 0 – 100 % ethyl acetate in hexanes to afford the title compound as a pale yellow solid (5.57 g, 44%).

LRMS: 252 $(M+H)^+$.

^1H NMR (DMSO-d_6, 400 MHz); 8.39 (1H, s) 7.59 (1H, d, J = 8.5 Hz) 7.48 (1H, d, J = 8.5 Hz) 4.46 (2H, s)

Preparation c-81

ethyl 2-[(6-bromopyridin-3-yl)methyl]tetrahydrofuran-2-carboxylate

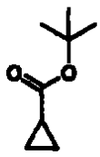


To a solution of ethyl tetrahydrofuran-2-carboxylate (52.9 mmol, 9.10 g, 1.5 eq.) cooled to –78 degrees C in THF (90 mL) was added dropwise a solution of 2 M lithium diisopropylamide (52.9 mmol, 1.5 eq.) in a mixture of heptane/THF/ethylbenzene. The enolate was allowed to form for one hour at the same low temperature whereupon a solution of 2-bromo-5-(bromomethyl)pyridine (35.3 mmol, 8.85 g, 1.0 eq.) in THF was added dropwise. The reaction was allowed to warm slowly to room temperature overnight. The reaction was quenched with saturated ammonium chloride. The mixture was extracted with ethyl acetate and the organic extract was washed with brine. The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo to yield a yellow oil. This crude product was purified on a Biotage Sp4 65i over a gradient of 5% to 95 % ethyl acetate in hexanes to afford a golden oil (8.70 g, 78%).
LRMS: 315 $(M+H)^+$.

^{1}H NMR (DMSO-d_6, 400 MHz): 8.21 (1 H, s) 7.40 - 7.49 (2 H, m) 3.94 (2 H, q, J=7.0 Hz) 3.71 - 3.85 (2 H, m) 3.05 - 3.11 (1 H, m) 2.91 - 2.97 (1 H, m) 2.38 - 2.47 (1 H, m) 1.83 - 2.09 (3 H, m) 1.09 (3 H, t, J=7.0 Hz)

Preparation c-82

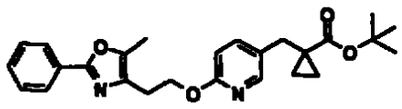
Cyclopropanecarboxylic acid tert-butyl ester



Concentrated sulfuric acid (3.45 mL, 62.7832 mmol) was added to a vigorously stirred suspension of anhydrous magnesium sulfate (30.1987 g, 251.1326 mmol) in dichloromethane (250 mL). The mixture was stirred for 15 minutes, after which cyclopropanecarboxylic acid (5 mL, 62.7832 mmol) and 2-methyl-propan-2-ol (30 mL, 313.9158 mmol) were added. The mixture was stoppered tightly and stirred at ambient temperature for 16 hours. The reaction mixture was then quenched with saturated aqueous sodium bicarbonate (450 mL) and stirred until all the magnesium sulfate had dissolved. The phases were separated and the organic phase washed with water (100 mL), saturdated aqueous sodium chloride (100 mL), dried (anhydrous magnesium sulfate), filtered and concentrated *in vacuo* to afford the pure ester (8.3921 g, 59.0162 mmol) as a colorless liquid.
^{1}H NMR ($CDCl_3$, 300 MHz): 1.45 (9H, s), 0.93-0.86 (3H, m), 0.79-0.73 (2H, m).

Preparation c-83

1-{6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridin-3-ylmethyl}-cyclopropanecarboxylic acid tert-butyl ester

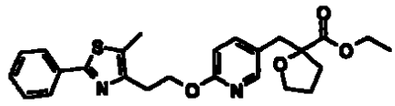


To a solution of diisopropylamine (0.14 mL, 0.9518 mmol) in dry tetrahydrofuran (2.4 mL), at 0 °C under an atmosphere of nitrogen, was added butyllithium (0.38 mL of a 2.5M solution in hexanes, 0.9518 mmol). The resulting solution was stirred for 30 minutes and then cooled to –50 °C. To this was added a solution of cyclopropanecarboxylic acid tert-butyl ester (0.1269 g, 0.8924 mmol) in dry tetrahydrofuran (1 mL) and stirring was continued for 2 hours. A solution of 5-Iodomethyl-2-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridine (0.25 g, 0.5949 mmol) in dry tetrahydrofuran (1 mL) was then added dropwise and the solution stirred for a further 3 hours. The reaction was quenched by the addition of saturated aqueous ammonium chloride (25 mL) and extracted with ethyl acetate (3 x 25 mL). The combined organic extracts were then dried (anhydrous magnesium sulfate), filtered and concentrated *in vacuo* to afford the crude product and remaining starting iodide. The residue was purified by flash column chromatography (hexanes to 60% ethyl acetate/hexanes) to yield the ester (0.0827 g, 32%), partially contaminated with started iodide, as a pale yellow solid.

LRMS (*m/z*): 435 $(M+H)^+$.

Preparation c-84

ethyl 2-({6-[2-(5-methyl-2-phenyl-1,3-thiazol-4-yl)ethoxy]pyridin-3-yl}methyl)tetrahydrofuran-2-carboxylate

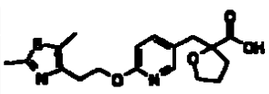
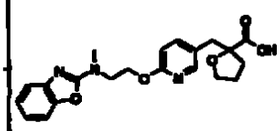
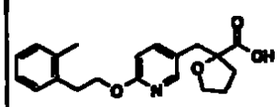
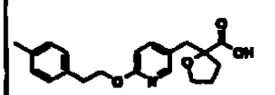


To an argon-purged solution of the bromopyridine (0.636 mmol) in toluene (12 mL) was added palladium (II) acetate (11.4 mg, 0.0508 mmol) and racemic-2-(di-t-butylphosphino)-1,1'-binaphthyl (25.4 mg, 0.0636 mmol). The activated complex was allowed to form over approximately ten minutes, at which point cesium carbonate (414 mg, 1.27 mmol) and the appropriate alcohol (0.956 mmol) were added. The mixture was heated to 115 °C and stirred at this temperature for 12-18 hours. The mixture was cooled to room temperature and filtered through a pad of silica. The filter pad was washed with 2-3 aliquots of ethyl acetate and the combined organic filtrates were combined and concentrated *in vacuo*. The

resulting residue was either purified by flash chromatography, or used without further purification

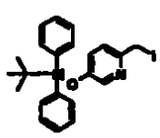
Preparations c-85 to c-88

Preparations c-85 to c-88 were prepared by procedures analogous to those used for Preparation c-84

Preparation #	Structure	^{1}H NMR	MS (*m/z*) (LR or HR)
c-85		(DMSO-d_6, 400 MHz)	for LR 420 $(M+H)^+$
c-86			
c-87			
c-88			

Preparation c-89

5-[(tert-butyl(diphenyl)silyl)oxy]-2-(iodomethyl)pyridine



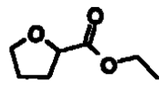
To a solution of 2-bromomethyl-5-(*tert*-butyl-diphenyl-silanyloxy)-pyridine (Schow, S. R.; Quinn DeJoy, S.; Wick, M. M.; Kerwar, S. S. *J. Org. Chem.* 1994, *59*, 6850-6852) (1.2692 g, 2.9763 mmol) in acetone (15 mL) was added sodium iodide (0.8922 g, 5.9526 mmol) and the resulting heterogeneous mixture stirred for 3 hours at ambient temperature. The reaction mixture was concentrated *in vacuo* and the resulting residue diluted with ethyl acetate (50 mL) and washed with water (50 mL). The organic layer was further washed with saturated aqueous sodium bicarbonate (50 mL) and saturated aqueous sodium thiosulfate (50 mL). The

combined aqueous layers were extracted with ethyl acetate (3x50 mL) and the combined organic extracts dried (anhydrous magnesium sulfate), filtered and concentrated *in vacuo* to afford the crude product. The residue was purified by flash column chromatography (hexanes to 20% ethyl acetate/hexanes) to yield a pale yellow oil (0.72 g, 51%). This compound was unstable to concentration and thus was used immediately.

LRMS (*m/z*): 474 $(M+H)^+$.

Preparation c-90

ethyl tetrahydrofuran-2-carboxylate



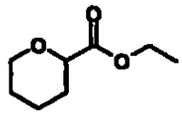
To a solution of tetrahydrofuran-2-carboxylic acid (20 g, 172.2356 mmol) in anhydrous ethanol (100 mL) was added concentrated sulfuric acid (0.46 mL). The resulting mixture was stirred at reflux for 16 hours and then allowed to cool to ambient temperature. To this was added water (100 mL) and extracted with diethyl ether (3x100 mL). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (2x50 mL), saturated aqueous sodium chloride (100 mL), dried (anhydrous magnesium sulfate), filtered and concentrated *in vacuo* to afford the pure product as a colorless liquid (22.5964 g, 91%).

LRMS (*m/z*): 145 $(M+H)^+$.

^{1}H NMR ($CDCl_3$, 300 MHz) 4.38 (1H, dd, J = 4.9, 8.1 Hz), 4.14 (2H, q, J = 7.2 Hz), 3.99-3.92 (1H, m), 3.88-3.81 (1H, m), 2.24-2.12 (1H, m), 2.00-1.79 (3H, m), 1.22 (3H, t, J = 7.2 Hz).

Preparation c-91

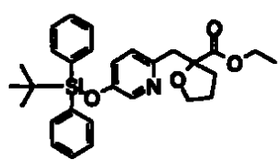
Tetrahydro-pyran-2-carboxylic acid ethyl ester



The above compound was prepared according to the procedure described in Rychnovsky, S. D.; Hata, T.; Kim, A. I.; Buckmelter, A. J. *Org. Lett.* 2001, *3*, 807-810.

Preparation c-92

ethyl 2-[(5-[(*tert*-butyl(diphenyl)silyl)oxy)pyridin-2-yl)methyl]tetrahydrofuran-2-carboxylate



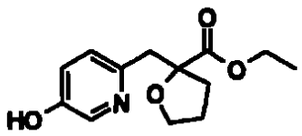
To a solution of ethyl tetrahydrofuran-2- carboxylate (Preparation 32) (1.0965 g, 7.604 mmol) in anhydrous tetrahydrofuran (7 mL) at –50 °C, under an atmosphere of nitrogen, was added sodium bis(trimethylsilyl)amide (7.6 mL of a 1.0M solution in tetrahydrofuran, 7.604 mmol) dropwise. The reaction mixture was stirred for 1 hour and then a solution of 5-(*tert*-butyl-diphenyl-allanyloxy)-2-iodomethyl-pyridine (Preparation 31) (0.72 g, 1.5208 mmol) in anhydrous tetrahydrofuran (7 mL) was added dropwise. The resulting solution was stirred at –50 °C for 2 hours and then quenched with saturated aqueous ammonium chloride (25 mL). This was then extracted with ethyl acetate (3x25 mL), dried (anhydrous magnesium sulfate), filtered and concentrated *in vacuo* to afford the crude product. The residue was purified by flash column chromatography (hexanes to 40% ethyl acetate/hexanes) to yield a colorless oil (0.2438 g, 33%).

LRMS (*m/z*): 490 $(M+H)^+$.

^{1}H NMR ($CDCl_3$, 300 MHz) 8.07 (1H, d, *J* = 2.5 Hz), 7.67-7.63 (4H, m), 7.41-7.31 (6H, m), 6.97 (1H, d, *J* = 8.5 Hz), 6.86 (1H, dd, *J* = 2.8, 8.5 Hz), 4.21 (2H, q, *J* = 7.2 Hz), 4.09 (2H, q, *J* = 7.2 Hz), 3.22 (1H, d, *J* = 13.9 Hz), 3.07 (1H, d, *J* = 13.9 Hz), 2.53-2.44 (1H, m), 2.31-2.15 (1H, m), 1.82-1.72 (1H, m), 1.60-1.46 (1H, m), 1.25 (3H, t, *J* = 7.2 Hz), 1.09 (9H, s).

Preparation c-93

ethyl 2-[(5-hydroxypyridin-2-yl)methyl]tetrahydrofuran-2-carboxylate



To a solution of ethyl 2-[(5-[[*tert*-butyl(diphenyl)allyl]oxy]pyridin-2-yl)methyl]tetrahydrofuran-2-carboxylate (Preparation c-92) (0.5118 g, 1.1677 mmol) in anhydrous tetrahydrofuran (10 mL) was added tetrabutylammonium fluoride (1.3 mL of a 1.0M solution in tetrahydrofuran) dropwise. The resulting mixture was stirred at ambient temperature for 1 hour and the volatiles removed *in vacuo*.. The residue was purified by flash column chromatography (50% ethyl acetate/hexanes to 10% methanol/ethyl acetate) to yield a colorless oil (0.2321 g, 79%).

LRMS (*m/z*): 252 $(M+H)^+$.

^{1}H NMR ($CDCl_3$, 300 MHz) 8.10 (1H, d, *J* = 2.3 Hz), 7.20 (1H, d, *J* = 8.5 Hz), 7.14 (1H, dd, *J* = 2.6, 8.5 Hz), 4.14 (2H, q, *J* = 7.2 Hz), 3.88 (2H, q, *J* = 7.8 Hz), 3.35 (1H, d, *J* = 13.9 Hz), 3.12 (1H, d, *J* = 13.9 Hz), 2.30-2.21 (1H, m), 2.04-1.94 (1H, m), 1.89-1.76 (1H, m), 1.75-1.63 (1H, m), 1.20 (3H, t, *J* = 7.2 Hz).

Preparation c-93a

Alternative preparation of ethyl 2-[(5-hydroxypyridin-2-yl)methyl]tetrahydrofuran-2-carboxylate

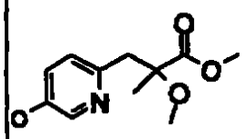
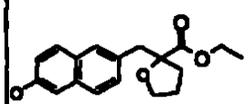
To a solution of 2-(5-benzyloxy-pyridin-2-ylmethyl)-tetrahydro-furan-2-carboxylic acid ethyl ester (0.5065 g, 1.7765 mmol) in dry ethanol (10 mL) was added palladium (0.0607 g, 10 wt. % on activated carbon). The resulting solution was heated at 45 °C under an atmosphere of hydrogen for 16 hours. After cooling to ambient temperature the solution was filtered through a 3" bed of Celite and washed with ethanol (100 mL). The filtrate was then concentrated *in vacuo* to afford the crude product which was used without further purification.

LRMS (*m/z*): 252 $(M+H)^+$.

^{1}H NMR ($CDCl_3$, 400 MHz): 8.10 (1H, d, *J* = 2.3 Hz), 7.20 (1H, d, *J* = 8.5 Hz), 7.14 (1H, dd, *J* = 2.6, 8.5 Hz), 4.14 (2H, q, *J* = 7.2 Hz), 3.88 (2H, q, *J* = 7.8 Hz), 3.35 (1H, d, *J* = 13.9 Hz), 3.12 (1H, d, *J* = 13.9 Hz), 2.30-2.21 (1H, m), 2.04-1.94 (1H, m), 1.89-1.76 (1H, m), 1.75-1.63 (1H, m), 1.20 (3H, t, *J* = 7.2 Hz).

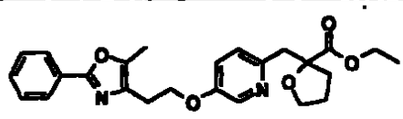
Preparations c-94 to c-95

Preparations c-94 to c-95 were prepared by general procedure for Preparation c-93

Prep #	Structure	^{1}H NMR	MS (*m/z*) (LR or HR)
c-94		($CDCl_3$, 400 MHz): 8.24 (1H, bs), 7.37-7.30 (1H, bm), 7.24-7.22 (1H, bm), 3.71 (3H, s), 3.28 (3H, s), 3.23-3.18 (2H, m), 1.40 (3H, s)	for LR 226 $(M+H)^+$
c-95		($CDCl_3$, 400 MHz): 7.64 (1H, d, *J* = 8.6 Hz), 7.61 (1H, s), 7.53 (1H, d, *J* = 8.6 Hz), 7.36 (1H, dd, *J* = 1.7, 8.6 Hz), 7.05-7.01 (2H, m), 5.32 (1H, s), 3.99-3.88 (2H, m), 3.34 (1H, d, *J* = 13.6 Hz), 3.11 (1H, d, *J* = 13.9 Hz), 2.33-2.27 (1H, m), 2.00-1.93 (1H, m), 1.89-1.77 (1H, m), 1.73-1.65 (1H, m), 1.19 (3H, t, *J* = 7.3 Hz)	for LR 301 $(M+H)^+$

Preparation c-96

ethyl 2-({5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridin-2-yl}methyl)tetrahydrofuran-2-carboxylate



To a solution of ethyl 2-[(5-hydroxypyridin-2-yl)methyl]tetrahydrofuran-2-carboxylate (Preparation c-93) (0.2321 g, 0.9237 mmol), 2-(5-methyl-2-phenyl-

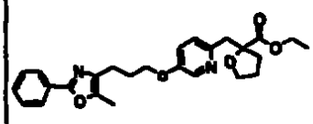
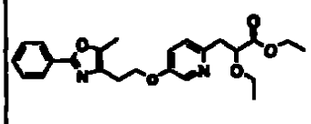
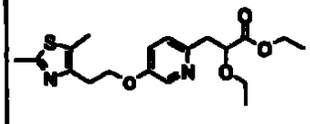
oxazol-4-yl)-ethanol (0.2065 g, 1.0161 mmol), and triphenylphosphine (0.3634 g, 1.3856 mmol) in anhydrous tetrahydrofuran (10 mL), under an atmosphere of nitrogen, was added a solution of diethyl azodicarboxylate (0.22 mL, 1.3856 mmol) in anhydrous tetrahydrofuran (1 mL) dropwise. The resulting solution was stirred at ambient temperature for 16 hours and the volatiles removed *in vacuo*. This residue was then purified by flash column chromatography (hexanes to 50% ethyl acetate/hexanes) to yield a pale yellow oil (0.2618 g, 65%).

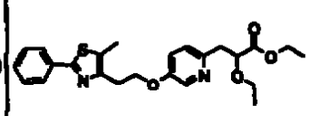
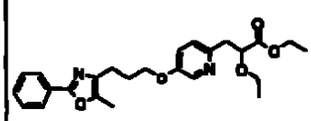
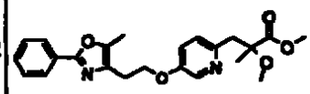
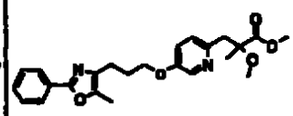
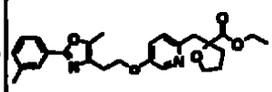
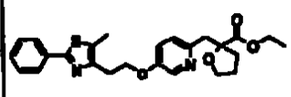
LRMS (*m/z*): 437 $(M+H)^+$.

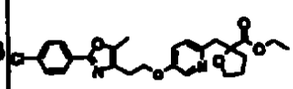
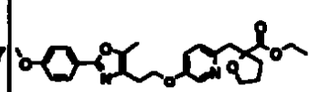
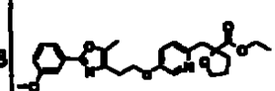
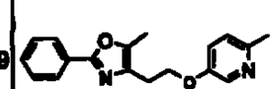
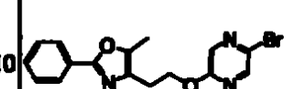
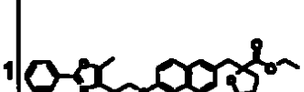
^{1}H NMR ($CDCl_3$, 300 MHz) 8.20 (1H, d, *J* = 2.8 Hz), 7.99 (1H, d, *J* = 2.5 Hz), 7.96 (1H, d, *J* = 1.7 Hz), 7.70-7.64 (1H, m), 7.49-7.39 (2H, m), 7.19 (1H, d, *J* = 8.5 Hz), 7.11 (1H, dd, *J* = 3.0, 8.5 Hz), 4.26 (2H, t, *J* = 6.6 Hz), 4.17 (2H, q, *J* = 7.2 Hz), 3.95-3.81 (2H, m), 3.33 (1H, d, *J* = 13.8 Hz), 3.16 (1H, d, *J* = 13.8 Hz), 2.98 (2H, t, *J* = 6.6 Hz), 2.37 (3H, s), 2.34-2.22 (1H, m), 2.09-2.00 (1H, m), 1.87-1.76 (1H, m), 1.72-1.62 (1H, m), 1.23 (3H, t, *J* = 7.2 Hz).

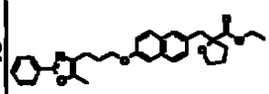
Preparations c-97 to c-112

Preparations c-97 to c-112 were prepared by general procedure for Preparation c-96

Preparation #	Structure	^{1}H NMR	MS (*m/z*) (LR or HR)
c-97		($CDCl_3$, 300 MHz): 8.19 (1H, d, *J* = 2.8 Hz), 7.97-7.93 (2H, m), 7.42-7.39 (3H, m), 7.18 (1H, d, *J* = 8.5 Hz), 7.10 (1H, dd, *J* = 8.5, 2.8 Hz), 4.16 (2H, q, *J* = 7.2 Hz), 3.98 (2H, t, *J* = 6.0 Hz), 3.92-3.82 (2H, m), 3.33 (1H, d, *J* = 13.8 Hz), 3.14 (1H, d, *J* = 13.9 Hz), 2.67 (2H, t, *J* = 6.0 Hz), 2.26 (3H, s), 2.19-2.10 (2H, m), 1.91-1.63 (4H, m), 1.22 (3H, t, *J* = 7.2 Hz)	for LR 451 $(M+H)^+$
c-98		($CDCl_3$, 400 MHz): 8.20 (1H, dd, *J* = 2.0, 1.5 Hz), 7.95 (2H, dd, *J* = 7.7, 1.9 Hz), 7.43-7.36 (3H, m), 7.10 (2H, d, *J* = 1.5 Hz), 4.25 (2H, t, *J* = 6.6 Hz), 4.23-4.13 (3H, m), 3.63-3.55 (1H, m), 3.37-3.27 (1H, m), 3.15-3.02 (2H, m), 2.97 (2H, t, *J* = 6.7 Hz), 2.35 (3H, s), 1.21 (3H, t, *J* = 7.2 Hz), 1.08 (3H, t, *J* = 7.1 Hz)	for LR 425 $(M+H)^+$
c-99		($CDCl_3$, 400 MHz): 8.19 (1H, dd, *J* = 2.0, 1.5 Hz), 7.08-7.07 (2H, m), 4.26-4.23 (3H, m), 4.16 (2H, q, *J* = 7.0 Hz), 3.63-3.56 (1H, m), 3.36-3.28 (1H, m), 3.15-3.02 (4H, m), 2.58 (3H, s), 2.34 (3H, s), 1.21 (3H, t, *J* = 7.1 Hz), 1.08 (3H, t, *J* = 7.0 Hz)	for LR 379 $(M+H)^+$

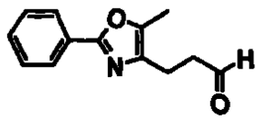
c-100		($CDCl_3$, 400 MHz): 8.22 (1H, dd, J = 2.4, 1.1 Hz), 7.86-7.83 (2H, m), 7.42-7.36 (3H, m), 7.11-7.10 (2H, m), 4.35 (2H, t, J = 6.8 Hz), 4.24 (1H, dd, J = 8.3, 5.1 Hz), 4.18 (2H, q, J = 7.1 Hz), 3.63-3.56 (1H, m), 3.36-3.28 (1H, m), 3.18 (2H, t, J = 6.8 Hz), 3.14 (1H, dd, J = 13.9, 5.1 Hz), 3.05 (1H, dd, J = 13.9, 8.3 Hz), 2.45 (3H, s), 1.22 (3H, t, J = 7.1 Hz), 1.09 (3H, t, J = 7.1 Hz)	for LR 441 $(M+H)^+$
c-101		($CDCl_3$, 400 MHz): 8.22 (1H, dd, J = 2.0, 1.5 Hz), 7.97-7.93 (2H, m), 7.43-7.37 (3H, m), 7.11-7.10 (2H, m), 4.25 (1H, dd, J = 8.6, 5.1 Hz), 4.18 (2H, q, J = 7.2 Hz), 3.99 (2H, t, J = 6.2 Hz), 3.64-3.56 (1H, m), 3.37-3.29 (1H, m), 3.14 (1H, dd, J = 13.9, 5.1 Hz), 3.06 (1H, dd, J = 13.9, 8.6 Hz), 2.68 (2H, t, J = 7.1 Hz), 2.26 (3H, s), 2.18-2.12 (2H, m), 1.22 (3H, t, J = 7.1 Hz), 1.09 (3H, t, J = 7.0 Hz)	for LR 439 $(M+H)^+$
c-102		($CDCl_3$, 400 MHz): 8.18 (1H, dd, J = 2.3, 1.3 Hz), 7.96 (2H, dd, J = 7.6, 2.0 Hz), 7.54-7.51 (3H, m), 7.10-7.08 (2H, m), 4.25 (2H, t, J = 6.7 Hz), 3.29 (3H, s), 3.15 (2H, s), 2.96 (2H, t, J = 6.7 Hz), 2.36 (3H, s), 2.32 (3H, s), 1.38 (3H, s)	for LR 411 $(M+H)^+$
c-103		($CDCl_3$, 400 MHz): 8.20 (1H, t, J = 7.8 Hz), 7.97-7.93 (2H, m), 7.44-7.38 (3H, m), 7.09 (2H, d, J = 7.8 Hz), 3.99 (2H, t, J = 6.1 Hz), 3.72 (3H, s), 3.30 (3H, s), 2.68 (2H, t, J = 7.1 Hz), 2.62 (2H, t, J = 6.7 Hz), 2.27 (3H, s), 2.18-2.12 (2H, m), 1.40 (3H, s)	for LR 425 $(M+H)^+$
c-104			for LR 451 $(M+H)^+$
c-105			for LR 453 $(M+H)^+$

c-106			for LR 471 $(M+H)^+$
c-107			for LR 467 $(M+H)^+$
c-108			for LR 467 $(M+H)^+$
c-109		($CDCl_3$, 300 MHz): 8.16 (1H, d, J = 2.6 Hz), 7.97-7.94 (2H, m), 7.48-7.39 (3H, m), 7.10 (1H, dd, J = 8.7, 3.0 Hz), 7.02 (1H, d, J = 8.5 Hz), 4.25 (2H, t, J = 6.7 Hz), 2.96 (2H, t, J = 6.7 Hz), 2.46 (3H, s), 2.36 (3H, s)	for LR 295 $(M+H)^+$
c-110		($CDCl_3$, 300 MHz); 8.16 (1H, d, J = 1.3 Hz), 7.96 (3H, dd, J = 7.4, 1.7 Hz), 7.41 (3H, dd, J = 5.3, 1.9 Hz), 4.58 (2H, t, J = 6.7 Hz), 2.98 (2H, t, J = 6.8 Hz), 2.34 (3H, s)	for LR 360 $(M)^-$
c-111		($CDCl_3$, 400 MHz): 7.99-7.97 (2H, m), 7.66 (1H, d, J = 8.8 Hz), 7.62-7.59 (2H, m), 7.45-7.35 (4H, m), 7.12-7.08 (2H, m), 4.35 (2H, t, J = 6.8 Hz), 4.16-4.09 (2H, m), 3.96-3.85 (2H, m), 3.32 (1H, d, J = 13.6 Hz), 3.11 (1H, d, J = 13.9 Hz), 3.04 (2H, t, J = 6.8 Hz), 2.40 (3H, s), 2.31-2.24 (1H, m), 1.99-1.76 (1H, m), 1.69-1.60 (1H, m), 1.18 (3H, t, J = 7.1 Hz)	for LR 486 $(M+H)^+$

c-112		($CDCl_3$, 400 MHz): 7.99-7.97 (2H, m), 7.67 (1H, d, J = 8.8 Hz), 7.61-7.59 (2H, m), 7.45-7.35 (4H, m), 7.12 (1H, dd, J = 2.3, 8.8 Hz), 7.08-7.07 (1H, d, J = 2.3 Hz), 4.16-4.06 (4H, m), 3.96-3.86 (2H, m), 3.33 (1H, d, J = 13.6 Hz), 3.11 (1H, d, J = 13.6 Hz), 2.74 (2H, t, J = 7.1 Hz), 2.32-2.16 (6H, m), 1.99-1.91 (1H, m), 1.86-1.77 (1H, m), 1.69-1.61 (1H, m), 1.19 (3H, t, J = 7.1 Hz)	for LR 500 $(M+H)^+$

Preparation c-113

3-(5-Methyl-2-phenyl-oxazol-4-yl)-propionaldehyde



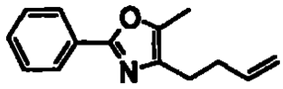
To a solution of 3-(5-methyl-2-phenyl-oxazol-4-yl)-propan-1-ol (1.0 g, 4.6026 mmol) in dichloromethane (20 mL) was added pyridinium chlorochromate (9.9213 g of ~20 wt. % on SiO_2, 9.2051 mmol). The resulting mixture was stirred under an atmosphere of nitrogen at ambient temperature for 16 hours and the volatiles removed under reduced pressure. The residue was purified by flash column chromatography (hexanes to ethyl acetate) to yield the pure aldehyde (0.4752 g, 48%) as a colorless oil.

LRMS (*m/z*): 216 $(M+H)^+$.

^1H NMR ($CDCl_3$, 300 MHz): 9.84 (1H, s), 7.96-7.93 (2H, m), 7.42-7.37 (3H, m), 2.85 (2H, dd, J = 6.0, 0.9 Hz), 2.80 (2H, d, J = 6.0 Hz), 2.33 (3H, s).

Preparation c-114

4-But-3-enyl-5-methyl-2-phenyl-oxazole



To a solution of methyl triphenylphosphonium iodide (1.7848 g, 4.4154 mmol) in dry tetrahydrofuran (95 mL), under an atmosphere of nitrogen at 0 °C, was added butyllithium (1.8 mL of a 2.5M solution in hexanes, 4.4154 mmol) dropwise. The suspension dissolved and the solution turned orange. After 10 minutes a solution of 3-(5-methyl-2-phenyl-oxazol-4-yl)-propionaldehyde (0.4752 g, 2.2077 mmol) in dry tetrahydrofuran (15 mL) was added dropwise and the solution allowed to warm to ambient temperature. After 16 hours, hexanes (200 mL) was added and the precipitate filtered off. The filtrate was then extracted with water (200 mL) and the organic phase dried (anhydrous magnesium sulfate), filtered, and concentrated *in vacuo* to afford the crude product. The residue was purified by flash column

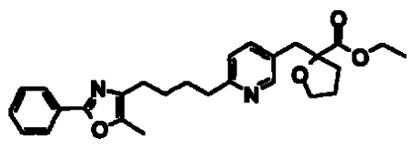
chromatography (hexanes to ethyl acetate) to yield the pure title compound (0.291 g, 62%) as a colorless oil.

LRMS (*m/z*): 214 $(M+H)^+$.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.99-7.96 (2H, m), 7.43-7.38 (3H, m), 5.93-5.79 (1H, m), 5.09-5.02 (1H, m), 5.00-4.95 (1H, m), 2.57 (2H, t, *J* = 7.4 Hz), 2.42 (2H, t, *J* = 7.4 Hz), 2.31 (3H, s).

Preparation c-115

2-[6-[4-(5-Methyl-2-phenyl-oxazol-4-yl)-butyl]-pyridin-3-ylmethyl]-tetrahydro-furan-2-carboxylic acid ethyl ester



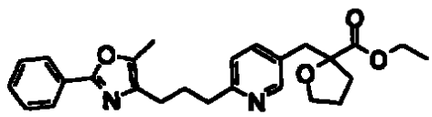
9-Borabicyclononane (5.5 mL of a 0.5M solution in tetrahydrofuran, 2.729 mmol) was added to a yellow solution of 4-but-3-enyl-5-methyl-2-phenyl-oxazole (0.291 g, 1.3845 mmol) in dry tetrahydrofuran (1.3 mL). The mixture was stirred at ambient temperature for 4 hours and then transferred to another flask containing 2-(6-bromo-pyridin-3-ylmethyl)-tetrahydro-furan-2-carboxylic acid ethyl ester (0.3297 g, 1.0496 mmol), palladium dichloride *bis*(diphenylphosphino)ferrocene (0.0857 g, 0.1050 mmol), cesium carbonate (0.9551 g, 2.9389 mmol), triphenylarsine (0.0322 g, 0.1050 mmol) in *N,N*-dimethylformamide (2.8 mL) and water (0.23 mL). The dark red mixture was stirred for 16 hours at ambient temperature under a nitrogen atmosphere. After cooling to 0 °C, the reaction was quenched with 2M aqueous sodium acetate (5 mL) and 30% aqueous hydrogen peroxide (2 mL). The resulting solution was stirred for 2 hours, diluted with water (25 mL), and extracted with ethyl acetate (4 x 50 mL). The combined organic extracts were washed with water (25 mL), dried (anhydrous magnesium sulfate), filtered, and concentrated *in vacuo* to give the crude product. The residue was purified by flash column chromatography (hexanes to ethyl acetate) to afford the title compound (0.2805 g, 60%) as pale yellow oil.

LRMS (*m/z*): 449 $(M+H)^+$.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.34 (1H, d, *J* = 1.9 Hz), 7.95 (2H, dd, *J* = 7.7, 1.9 Hz), 7.52 (1H, dd, *J* = 8.0, 2.2 Hz), 7.42-7.36 (3H, m), 7.04 (1H, d, *J* = 7.9 Hz), 4.13 (2H, q, *J* = 7.2 Hz), 3.96-3.84 (2H, m), 3.16 (1H, d, *J* = 13.9 Hz), 2.90 (1H, d, *J* = 13.9 Hz), 2.77 (2H, t, *J* = 7.3 Hz), 2.50 (2H, t, *J* = 6.9 Hz), 2.31-2.19 (1H, m), 2.28 (3H, s), 1.92-1.64 (7H, m), 1.20 (3H, t, *J* = 7.2 Hz).

Preparation c-116

2-[6-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-pyridin-3-ylmethyl]-tetrahydro-furan-2-carboxylic acid ethyl ester



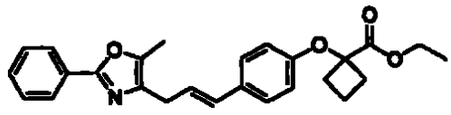
9-Borabicyclononane (4.2 mL of a 0.5M solution in tetrahydrofuran, 2.07 mmol) was added to a yellow solution of 4-allyl-5-methyl-2-phenyl-oxazole (0.21 g, 1.04 mmol) in dry tetrahydrofuran (1 mL). The mixture was stirred at ambient temperature for 4 hours and then transferred to another flask containing 2-(6-bromo-pyridin-3-ylmethyl)-tetrahydro-furan-2-carboxylic acid ethyl ester (0.25 g, 0.80 mmol), palladium dichloride *bis*(diphenylphosphino)ferrocene (0.07 g, 0.1 mmol), cesium carbonate (0.72 g, 2.90 mmol), triphenylarsine (0.02 g, 0.1 mmol) in *N,N*-dimethylformamide:water (4:1, 2.63 mL). The dark red mixture was stirred for 16 hours at ambient temperature under a nitrogen atmosphere. After cooling to 0 °C, the reaction was quenched with 2M aqueous sodium acetate (4.7 mL) and 30% aqueous hydrogen peroxide (1.7 mL). The resulting solution was stirred for 2 hours, diluted with water (20 mL), and extracted with ethyl acetate (4 x 50 mL). The combined organic extracts were washed with water (20 mL), dried (anhydrous magnesium sulfate), filtered, and concentrated *in vacuo* to give the crude product. The residue was purified by flash column chromatography (40% to 90% ethyl acetate/hexanes) to afford the title compound (0.20 g, 57%) as a colorless oil.

LRMS (*m/z*): 435 $(M+H)^+$.

^{1}H NMR (Dimethyl sulfoxide-d_6, 400 MHz): 8.35 (1H, s), 7.96 (2H, d, *J* = 7.9 Hz), 7.55 (1H, d, *J* = 8.3 Hz), 7.39 (3H, t, *J* = 5.9 Hz), 7.09 (1H, d, *J* = 8.1 Hz), 3.91 (2H, m), 3.80 (2H, t, *J* = 10.9 Hz), 3.17 (1H, d, *J* = 14.0 Hz), 2.91 (1H, d, J = 13.94 Hz), 2.81 (2H, t), 2.53 (2H, t, *J* = 7.3 Hz), 2.28 (3H, s), 2.09 (2H, d, *J* = 7.5 Hz), 1.87 (4H, d, *J* = 10.9 Hz), 1.23 (3H, m).

Preparation c-117

Ethyl 1-[4-[(1*E*)-3-(5-methyl-2-phenyl-1,3-oxazol-4-yl)prop-1-en-1-yl]phenoxy]cyclobutanecarboxylate



A mixture of $Pd(OAc)_2$ (12 mg, 0.05 mmol) and Ph_3P (26 mg, 0.05 mmol) in toluene (2 mL) was stirred under nitrogen at room temperature for 1 hour and followed by the addition of Et_3N (2 mL) and a solution of 4-allyl-5-methyl-2-phenyl-1,3-oxazole (100 mg, 0.50 mmol) and ethyl 1-(4-iodophenoxy)cyclobutanecarboxylate (173 mg, 0.50 mmol) in toluene (2 mL). The resulting reaction solution was heated at 80 °C

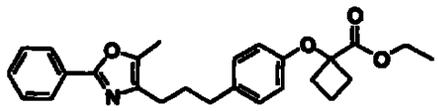
under nitrogen for 17 hours and cooled to room temperature. After solvent removal, the residue was partitioned between EtOAc and brine. The separated organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give the crude product as brown oil. Purification by silica gel column with 20% EtOAc in hexane gave 85 mg (41%) of yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) 1.19 (t, 3 H), 1.98 (m, 2 H), 2.38 (s, 3 H), 2.43 (m, 2 H), 2.72 (m, 2 H), 3.41 (d, 2 H), 4.18 (q, 2 H), 6.20 (td, 1 H), 6.40 (d, 1 H), 6.80 (d, 2 H), 7.25 (d, 2 H), 7.40 (d, 3 H), 8.00 (d, 2 H).

LRMS (*m/z*): 418 $(M+H)^+$.

Preparation c-118

Ethyl 1-{4-[3-(5-methyl-2-phenyl-1,3-oxazol-4-yl)propyl]phenoxy}cyclobutane-carboxylate



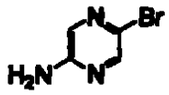
Ethyl1-{4-[(1*E*)-3-(5-methyl-2-phenyl-1,3-oxazol-4-yl)prop-1-en-1-yl]phenoxy}cyclobutanecarboxylate (85 mg, 0.20 mmol) was dissolved in MeOH (5 mL) and followed by the addition of 10% Pd/C (15 mg). The mixture was stirred at room temperature for 16 hours with a balloon, full of hydrogen gas, attached to the flask. The mixture was filtered through a pad of Celite and the cake was rinsed with MeOH. The filtrate was concentrated to give 85 mg (100%) of yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) 1.19 (t, 3 H), 1.92 - 2.02 (m, 4 H), 2.27 (s, 3 H), 2.39 - 2.51 (m, 4 H), 2.60 (t, 2 H), 2.66 - 2.77 (m, 2 H), 4.19 (q, 2 H), 6.60 (d, 2 H), 7.05 (d, 2 H), 7.36 - 7.47 (m, 3 H), 7.98 (dd, 2 H).

LRMS (*m/z*): 420 $(M+H)^+$.

Preparation c-119

5-Bromo-pyrazin-2-ylamine



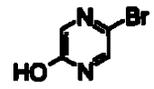
To a solution of pyrazin-2-ylamine (2.0 g, 21.03 mmol) in dry dichloromethane (120 mL) at 0 °C, was added *N*-bromosuccinimide (3.74 g, 21.03 mmol) slowly to maintain the internal temperature below 0 °C. The mixture was stirred at the same temperature for 24 hours, and then washed with saturated aqueous sodium bicarbonate (30 mL) and water (30 mL). The combined aqueous extracts were extracted with dichloromethane (3 x 100 mL). The combined organic extracts were dried (anhydrous magnesium sulfate), filtered, and concentrated *in vacuo* to afford the crude product. The residue was purified by flash column chromatography (10% to 50% ethyl acetate/hexanes) to yield the title compound (2.57 g, 70%) as a yellow solid.

LRMS (*m/z*): 174 $(M)^-$.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.08 (1H, d, *J* = 1.3 Hz), 7.76 (1H, d, *J* = 1.3 Hz).

Preparation c-120

5-Bromo-pyrazin-2-ol

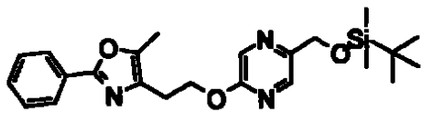


Sodium nitrite (1.35 g, 19.53 mmol) was added portionwise to concentrated sulfuric acid (9.8 mL) at 0 °C. The mixture was heated at 50 °C until all of the sodium nitrite had dissolved and the mixture was again cooled to 0 °C. A solution of 5-bromo-pyrazin-2-ylamine (2.57 g, 14.88 mmol) in concentrated sulfuric acid (14.7 mL) was added dropwise to the nitronium solution at 0 °C. The ice bath was removed, the mixture warmed to ambient temperature and stirred for 15 minutes before heating to 45 °C for seven minutes. After cooling to ambient temperature, the mixture was poured slowly with precaution into crushed ice water (100 mL). The aqueous phase was neutralized to pH 4 with 20% aqueous sodium hydroxide then extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with water (50 mL), dried (anhydrous magnesium sulfate), filtered, and evaporated to afford the title compound (1.88 g, 73%) as a yellow solid.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.07 (1H, s), 7.82 (1H, d, *J* = 3.0 Hz).

Preparation c-121

2-(tert-Butyl-dimethyl-silanyloxymethyl)-5-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyrazine



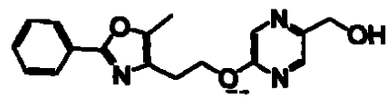
To a solution of 2-bromo-5-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyrazine (0.50 g, 1.39 mmol) and *tert*-butyl-dimethyl-tributylstannanylmethoxy-silane (0.91 g, 2.08 mmol) in dry 1,4-dioxane (8 mL) was added tetrakistriphenylphosphine(0) palladium (0.16 g, 0.14 mmol). The mixture was degassed three times and then heated at 120 °C for 22 hours. After cooling to ambient temperature the mixture was diluted with diethyl ether (10 mL) and then quenched with saturated aqueous potassium fluoride (5 mL). The resulting mixture was stirred for 30 minutes and then extracted with ethyl acetate (3 x 50 mL). The organic phase was washed with water (30 mL), dried (anhydrous magnesium sulfate), filtered, and evaporated to afford the title compound without any further purification.

LRMS (*m/z*): 426 $(M+H)^+$.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.20 (1H, s), 8.09 (1H, s), 7.97 (2H, d, J = 7.4 Hz), 7.41 (3H, d, J = 5.3 Hz), 4.78 (2H, s), 4.58 (2H, d, J = 6.6 Hz), 2.98 (2H, s), 2.34 (3H, s), 0.97 (2H, m), 0.14 (6H, m).

Preparation c-122:

{5-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyrazin-2-yl}-methanol



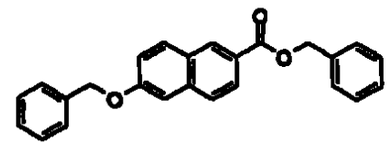
Tetrabutylammonium fluoride (2.8 mL of a 1M solution in tetrahydrofuran, 2.78 mmol) was added dropwise to a solution of 2-(*tert*-butyl-dimethyl-silanyloxymethyl)-5-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyrazine (~1.39 mmol) in dry tetrahydrofuran (20 mL). The mixture was stirred at ambient temperature for 16 hours and then quenched with water (1 mL), and acidified to pH 5 with 1M aqueous acetic acid solution. The organics were removed *in vacuo* and the aqueous phase extracted with dichloromethane (3 x 50 mL). The combined organic extracts were dried (anhydrous magnesium sulfate), filtered, and concentrated *in vacuo* to afford the title compound (0.0928 g, 21%).

LRMS (*m/z*): 312 $(M+H)^+$.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.12 (2H, s), 8.05 (2H, d, J = 6.0 Hz), 7.40 (3H, d, J = 6.0 Hz), 4.72 (2H, s), 4.59 (2H, t, J = 6.0 Hz), 2.99 (2H, t, J = 6.0 Hz), 2.33 (3H, s).

Preparation c-123

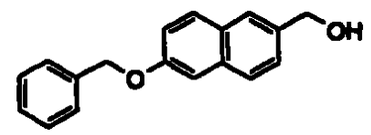
6-Benzyloxy-naphthalene-2-carboxylic acid benzyl ester



The above compound was prepared according to the procedure described in Inui, S.; Suzuki, T.; Iimura, N.; Iwane, H.; Nohira, H. *Mol. Cryst. Liq. Cryst. Sci. Technol. Sect. A.* 1994, *239*, 1-10.

Preparation c-124

(6-Benzyloxy-naphthalen-2-yl)-methanol



To a solution of 6-benzyloxy-naphthalene-2-carboxylic acid benzyl ester (7.09 g, 19.24 mmol) in dry tetrahydrofuran (60 mL), under an atmosphere of nitrogen at 0 °C, was added diisobutylaluminum hydride (58 mL of a 1.0M solution in tetrahydrofuran, 57.73 mmol). The resulting mixture was allowed to warm to

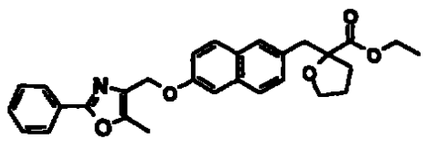
ambient temperature and stirred for 16 hours. An solution of citric acid (19 g) in water (40 mL) was added dropwise (CAUTION!: strong exotherm). The aqueous layer was then extracted with ethyl acetate (3 x 50 mL) and the combined organic extracts washed with saturated aqueous sodium chloride (50 mL), dried (anhydrous magnesium sulfate), and concentrated *in vacuo* to afford the crude product. The residue was purified by flash column chromatography (hexanes to ethyl acetate) to yield the title compound (4.37 g, 86%) as a white solid.

LRMS (*m/z*): 287 $(M+Na)^+$.

^1H NMR ($CDCl_3$, 400 MHz): 7.76-7.72 (3H, m), 7.50-7.33 (6H, m), 7.25-7.23 (2H, m), 5.16 (2H, s), 4.62 (2H, d, J = 6.1 Hz).

Preparation c-125

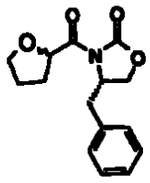
2-[6-(5-Methyl-2-phenyl-oxazol-4-ylmethoxy)-naphthalen-2-ylmethyl]-tetrahydro-furan-2-carboxylic acid ethyl ester



A heterogeneous mixture of 2-phenyl-4-(chloromethyl)-5-methyloxazole (0.133 g, 0.639 mmol), 2-(6-hydroxy-naphthalen-2-ylmethyl)-tetrahydro-furan-2-carboxylic acid ethyl ester (0.192 g, 0.639 mmol), and cesium carbonate (0.521 g, 1.59 mmol) in dry acetonitrile (2 mL) was heated (in a microwave) at 140 °C for 10 minutes. A second portion of 2-phenyl-4-(chloromethyl)-5-methyloxazole (0.5 eq.) was added and the mixture heated at 200 °C for a further 20 minutes. The reaction mixture was filtered through Celite and washed with acetonitrile (200 mL). The filtrate was concentrated *in vacuo* and the residue purified by flash column chromatography (hexanes to ethyl acetate) to yield the title compound (0.180 g, 60%) as a colorless oil.

Preparation c-126

(4*S*)-4-benzyl-3-(tetrahydrofuran-2-ylcarbonyl)-1,3-oxazolidin-2-one

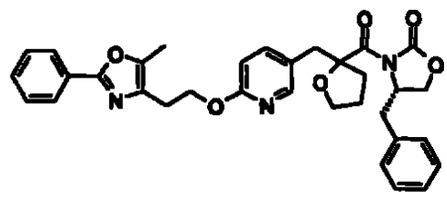


n-Butyllithium (22.6 mL of a 2.5M solution in hexanes, 56.4 mmol) was added dropwise to a solution of (4*S*)-4-benzyl-1,3-oxazolidin-2-one (10.0 g, 56.4 mmol) in tetrahydrofuran (200 mL) at –78°C. The mixture was stirred for 30 minutes then a solution of tetrahydrofuran-2-carbonyl chloride (9.12 g, 67.7 mmol) in tetrahydrofuran (25 mL) was added. The mixture was stirred at -78°C for 30

minutes, warmed to 0°C over 1 hour and quenched with saturated ammonium chloride solution. The Mixture was extracted with ethyl acetate and the organic phase was washed with brine, dried over magnesium sulfate, filtered and evaporated. The residue was purified by flash column chromatography (1:3 then 1:2 ethyl acetate:hexanes) to yield the title compound as a ca. 1:1 mixture of diastereoisomers as a colorless oil (15.0 g, 97%).

Preparation c-127

(4S)-4-benzyl-3-[[2-[(6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridin-3-yl]methyl]tetrahydrofuran-2-yl]carbonyl]-1,3-oxazolidin-2-one



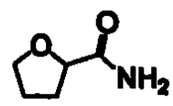
Sodium (bis)trimethylsilyl amide (3.57 mL of 1M solution in tetrahydrofuran, 3.57 mmol) was added dropwise to a solution of (4S)-4-benzyl-3-(tetrahydrofuran-2-ylcarbonyl)-1,3-oxazolidin-2-one (0.983 g, 3.57 mmol) in anhydrous tetrahydrofuran (6 mL) at –50 °C. The mixture was stirred for 45 minutes and then a solution of 5-(iodomethyl)-2-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridine (Preparation 28) (0.500 g, 1.19 mmol) in anhydrous tetrahydrofuran (6 mL) was added dropwise. The resulting mixture was stirred at –50 °C for 1.5 hours then quenched with saturated aqueous ammonium chloride and warmed to ambient temperature. The mixture was extracted with ethyl acetate and the organic phase dried (anhydrous magnesium sulfate), filtered and evaporated. The residue was purified by flash column chromatography (1:1 ethyl acetate:hexanes) to yield the title compound as a single diastereoisomer as a colorless oil (0.617 g, 90%).

LRMS (*m/z*): 568 $(M+H)^+$.

^{1}H NMR ($CDCl_3$, 300 MHz) 8.01 (1H, s), 7.96 (2H, m), 7.81 (1H, dd, *J* = 2.5, 8.5 Hz), 7.40 (3H, m), 7.28 (3H, m), 7.17 (1H, m), 6.64 (1H, d, *J* = 8.6 Hz), 4.55 (3H, m), 4.18 (2H, m), 3.90 (1H, m), 3.79 (1H, m), 3.27 (1H, d, *J* = 14 Hz), 3.20 (1H, m), 3.13 (1H, d, *J* = 14 Hz), 2.96 (2H, t, *J* = 6.8 Hz), 2.79 (1H, m), 2.32 (3H, s), 2.34 (3H, m), 2.11 (1H, m), 1.73 (1H, m), 1.54 (1H, m)

Preparation c-128

Tetrahydro-furan-2-carboxylic acid amide



To a solution of tetrahydro-furan-2-carboxylic acid (2.42 g, 20.82 mmol) in anhydrous tetrahydrofuran (120 mL), under an atmosphere of nitrogen at 0 °C, was

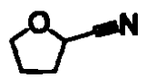
added triethylamine (8.5 mL, 61.23 mmol) and ethyl chloroformate (2.4 mL, 25.10 mmol). White precipitation formed after the addition of ethyl chloroformate and the resulting mixture stirred for 45 minutes at 0 °C. Ammonia gas was bubbled into the solution for 2 hours and the gas source removed. The reaction mixture was then allowed to warm to ambient temperature and stirred for 16 hours. The solution was adjusted to pH 1 by addition of 1N hydrochloric acid, and then extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried (anhydrous magnesium sulfate), filtered, and concentrated *in vacuo* to give the crude product. The residue was purified by flash column chromatography (hexanes to 10% ethyl acetate/hexanes) to afford the title compound (0.97 g, 41%) as a white solid.

LRMS (*m/z*): 116 $(M+H)^+$.

^{1}H NMR ($CDCl_3$, 300 MHz): 4.35 (1H, dd, *J* = 8.5, 5.8 Hz), 3.92 (2H, m), 2.18 (2H, m), 1.90 (2H, m).

Preparation c-129

Tetrahydro-furan-2-carbonitrile

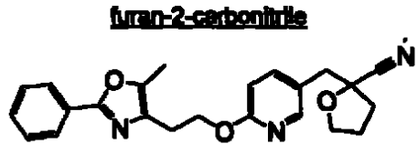


Trifluoroacetic anhydride (1.55 g, 7.38 mmol) was added slowly, with a rate of one drop every 10 seconds, to an ice-cold solution (0 °C) of tetrahydro-furan-2-carboxylic acid amide (0.77 g, 6.71 mmol) and pyridine (1.06 g, 13.42 mmol) in anhydrous 1,4-dioxane (10 mL). The addition of trifluoroacetic anhydride was monitored to keep the internal temperature below 5 °C and was completed after 20 minutes. The resulting mixture was allowed to warm to ambient temperature, and stirred for 3 hours. Chloroform (100 mL) was added to the mixture, and then extracted with water (30 mL) and saturated aqueous sodium chloride (20 mL). The organic extracts were dried (anhydrous magnesium sulfate), filtered, and concentrated *in vacuo* to give the crude product. The residue was purified by flash column chromatography (hexanes to 25% ethyl acetate/hexanes) to afford the title compound (0.51 g, 62%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): 4.70 (1H, m), 3.96 (2H, m), 2.24 (2H, m), 2.08 (2H, m).

Preparation c-130

2-[6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridin-3-ylmethyl]-tetrahydro-furan-2-carbonitrile



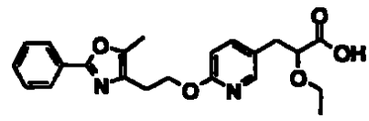
Sodium bis(trimethylsilyl)amide (1.8 mL, 1.79 mmol) was added to a solution of tetrahydro-furan-2-carbonitrile (0.17 g, 1.79 mmol) in anhydrous tetrahydrofuran (6 mL) under an atmosphere of nitrogen at –78 °C. The resulting yellow solution was stirred for 60 minutes, and then a solution of 5-iodomethyl-2-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridine (0.25 g, 0.596 mmol) in anhydrous tetrahydrofuran (3 mL) was added to the enolate solution. The mixture was stirred at –78 °C for 1.5 hours, and quenched with saturated aqueous ammonium chloride (5 mL). The aqueous phase was extracted with ethyl acetate (3 x 50 mL), and the combined organic extracts washed with water (30 mL), dried (anhydrous magnesium sulfate), filtered, and concentrated *in vacuo* to give the crude product. The residue was purified by flash column chromatography (7% to 45% ethyl acetate/hexanes) to afford the title compound (0.11 g, 46%) as a white solid.

LRMS (*m/z*): 390 $(M+H)^+$.

^{1}H NMR ($CDCl_3$, 300 MHz); 8.03 (1H, d, *J* = 2.5 Hz), 7.95 (2H, m), 7.56 (1H, dd, *J* = 8.5, 2.5 Hz), 7.40 (3H, m), 6.68 (1H, d, *J* = 8.5 Hz), 4.54 (2H, m), 3.96 (2H, m), 3.00 (4H, m), 2.33 (5H, d, *J* = 3.2 Hz), 1.92 (2H, m).

Example D-1

2-ethoxy-3-[6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridin-3-yl]propanoic acid

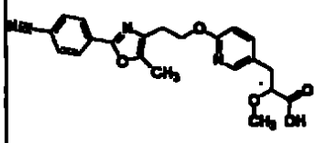
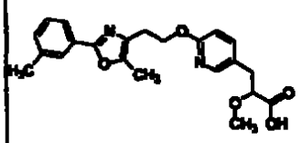
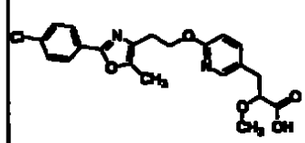
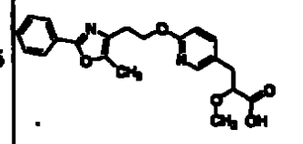


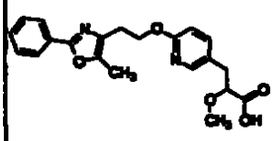
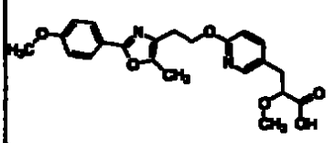
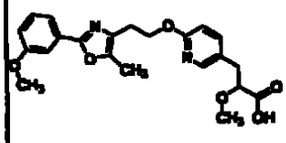
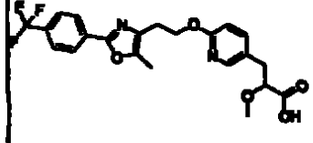
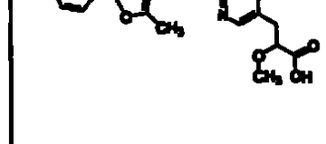
Lithium hydroxide monohydrate (180 mg, 4.31 mmol) was added to a solution of ethyl 2-ethoxy-3-[6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridin-3-yl]propanoate (183 mg, 0.431 mmol) in a mixture of tetrahydrofuran:methanol:water (1:1:1, 6 mL). The mixture was stirred 18 hours then the volatile components were removed by evaporation. The aqueous phase was acidified with 3M hydrochloric acid and extracted with ethyl acetate. The organic phase was washed with brine, dried over magnesium sulfate, filtered and evaporated. The residue was purified twice by flash column chromatography (98:2 dichloromethane:methanol) to yield the title compound as a colorless glass (31 mg)
LRMS (*m/z*): 396 $(M)^+$.
^{1}H NMR ($CDCl_3$, 300 MHz) 7.99 (3H, m), 7.50 (1H, m), 7.40 (3H, m), 6.65 (1H, m), 4.50 (2H, t, *J* = 7 Hz), 4.01 (1H, m), 3.64 (1H, m), 3.42 (1H, m), 2.98 (4H, m), 2.34 (3H, s), 1.16 (3H, t, *J* = 7 Hz).

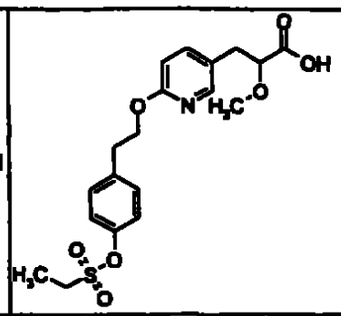
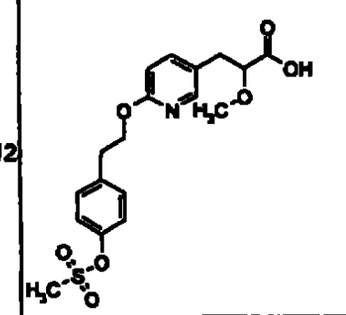
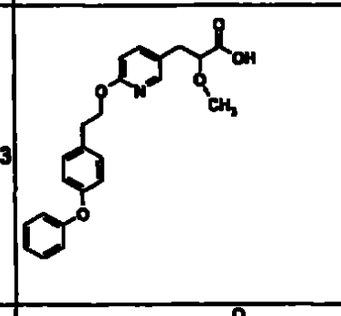
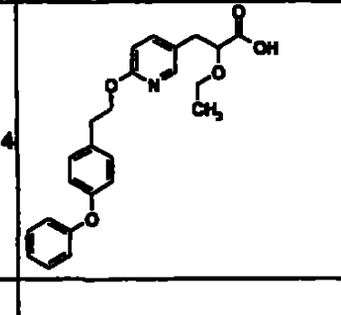
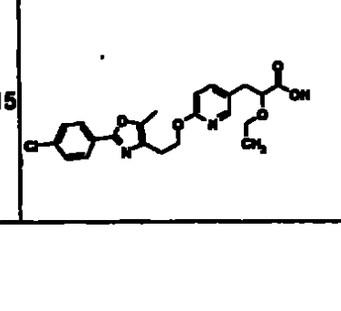
Examples D-2 to D-45

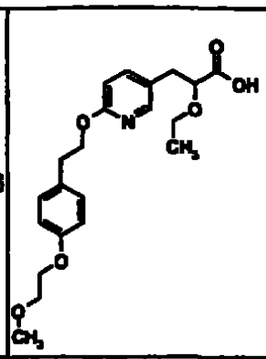
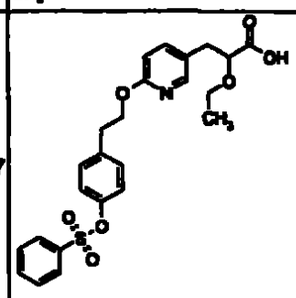
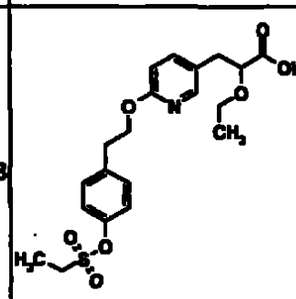
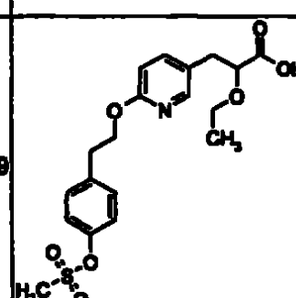
Examples D-2 to D-45 were prepared by procedures analogous to those used for Example D-1 by stirring a solution of the ester with sodium or lithium hydroxide in

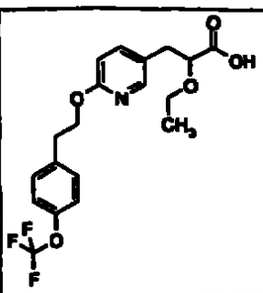
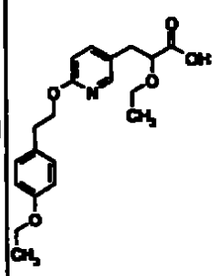
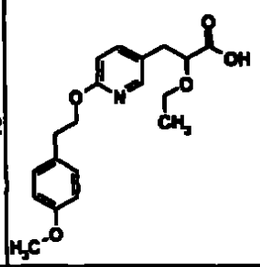
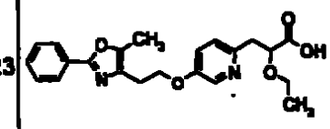
aqueous methanol, aqueous ethanol, aqueous tetrahydrofuran or mixtures thereof at temperatures between 20 °C and 75°C.

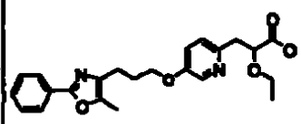
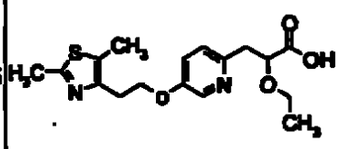
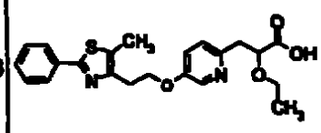
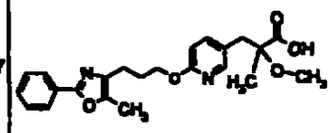
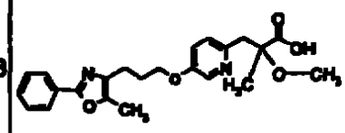
Ex #	Structure	^{1}H NMR	MS (*m/z*) LR/HR	Analysis
D-2		^{1}H NMR (DMSO-d_6, 400 MHz) : 8.05 (2H, d, *J* = 8.6 Hz), 7.96-7.94 (3H, m), 7.55 (1H, dd, *J* = 8.3 and 2.3 Hz), 6.70 (1H, d, *J* = 8.3 Hz), 4.45 (2H, t, *J* = 6.6 Hz), 3.89 (1H, dd, *J* = 7.6 and 5.1 Hz), 3.22 (3H, s), 2.95-2.87 (3H, m), 2.80 (1H, dd, *J* = 14.2 and 7.6 Hz), 2.35 (3H, s)	for LR 408 $(M+H)^+$	
D-3		^{1}H NMR (DMSO-d_6, 400 MHz) : 7.96 (1H, d, *J* = 2.3 Hz), 7.73 (1H, s), 7.69 (1H, d, *J* = 7.8 Hz), 7.55 (1H, dd, *J* = 8.6 and 2.3 Hz), 7.37 (1H, t, *J* = 7.8 Hz), 7.26 (1H, d, *J* = 7.1 Hz), 6.70 (1H, d, 8.3 Hz), 4.44 (2H, t, *J* = 6.8 Hz), 3.89 (1H, dd, *J* = 8.1 and 4.8 Hz), 3.22 (3H, s), 2.92-2.88 (3H, m), 2.80 (1H, d, *J* = 14.7 and 8.1 Hz), 2.36 (3H, s), 2.31 (3H, s)	Calcd for $C_{22}H_{25}N_2O_6$ 397.1758. Found: 397.1775	Calcd for $C_{22}H_{24}N_2O_6$0.5$H_2$0 C 65.17 H 6.22 N 6.91. Found: C 65.03 H 6.10 N 7.07
D-4		^{1}H NMR (DMSO-d_6, 400 MHz) : 7.98 (1H, d, *J* = 1.8 Hz), 7.92 (2H, d, *J* = 8.6 Hz), 7.58-7.55 (3H, m), 6.72 (1H, d, *J* = 8.6 Hz), 4.46 (2H, t, *J* = 6.6 Hz), 3.91 (1H, dd, *J* = 7.8 and 4.6 Hz), 3.24 (3H, s), 2.94-2.89 (3H, m), 2.82 (1H, dd, *J* = 14.4 and 7.6 Hz), 2.33 (3H, s).	Calcd for $C_{21}H_{22}ClN_2O_6$ 417.1212. Found: 417.1232	
D-5		^{1}H NMR (DMSO-d_6, 400 MHz) : 12.71 (1H, s), 7.96 (1H, d, *J* = 2.3 Hz), 7.90 (2H, dd, *J* = 7.6 and 2.0), 7.55 (1H, dd, *J* = 8.6 and 2.3 Hz), 7.51-7.46 (3H, m), 6.71 (1H, d, *J* = 8.6 Hz), 4.44 (2H, t, *J* = 6.6 Hz), 3.89 (1H, dd, *J* = 7.6 and 5.1 Hz), 3.22 (3H, s), 2.92-2.88 (3H, m), 2.80 (1H, dd, *J* = 14.2 and 7.6 Hz), 2.32 (3H, s).		Calcd for $C_{21}H_{22}N_2O_6$0.1$H_2$0 C 65.65 H 5.82 N 7.29. Found: C 65.45 H 5.92 N 7.26.

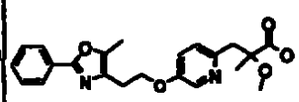
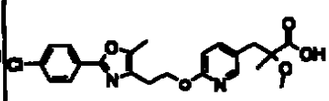
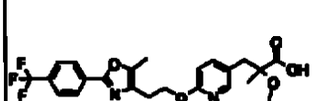
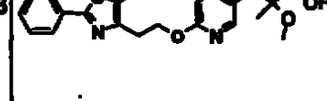
D-6		^{1}H NMR (DMSO-d_6, 400 MHz) : 12.81 (1H, s), 7.96 (1H, d, J = 2.0 Hz), 7.90 (2H, dd, J = 7.7 and 1.9), 7.55 (1H, dd, J = 8.6 and 2.3 Hz), 7.51-7.46 (3H, m), 6.70 (1H, d, J = 8.6 Hz), 4.44 (2H, t, J = 6.8 Hz), 3.88 (1H, dd, J = 7.8 and 4.8 Hz), 3.22 (3H, s), 2.92-2.87 (3H, m), 2.80 (1H, dd, J = 14.2 and 7.8 Hz), 2.32 (3H, s).		Calcd for $C_{21}H_{22}N_2O_5$0.25$H_2$0 C 65.19 H 5.86 N 7.24. Found: C 65.19 H 5.80 N 7.03
D-7		^{1}H NMR (DMSO-d_6, 400 MHz) : 12.54 (1H, s), 7.96 (1H, d, J = 2.0 Hz), 7.83 (2H, d, J = 9.1), 7.55 (1H, dd, J = 8.6 and 2.3 Hz), 7.03 (2H, d, J = 8.8 Hz), 6.70 (1H, d, J = 8.6 Hz), 4.43 (2H, t, J = 6.8 Hz), 3.90 (1H, dd, J = 7.8 and 4.8 Hz), 3.80 (3H, s), 3.22 (3H, s), 2.92-2.86 (3H, m), 2.80 (1H, dd, J = 14.7 and 7.8 Hz), 2.29 (3H, s)	Calcd for $C_{22}H_{25}N_2O_6$ 413.1707. Found: 413.1717	
D-8		^{1}H NMR (DMSO-d_6, 400 MHz) : 12.77 (1H, s), 7.96 (1H, d, J = 2.3 Hz), 7.55 (1H, dd, J = 8.3 and 2.3), 7.48 (1H, d, J = 7.8 Hz), 7.41 (1H, d, J = 8.1 Hz), 7.39-7.37 (1H, m), 7.04 (1H, dd, J = 8.1 and 2.5 Hz), 6.71 (1H, d, J = 8.6 Hz), 4.44 (2H, t, J = 6.8 Hz), 3.89 (1H, dd, J = 7.8 and 4.8 Hz), 3.81 (3H, s), 3.22 (3H, s), 2.92-2.88 (3H, m), 2.80 (1H, dd, J = 14.4 and 8.0 Hz), 2.31 (3H, s).	Calcd for $C_{22}H_{25}N_2O_6$ 413.1707. Found: 413.1715	
D-9		^{1}H NMR (DMSO-d_6, 400 MHz) : 12.70 (1H, s), 8.04 (2H, d, J = 8.1 Hz), 7.91 (1H, d, J = 2.0), 7.80 (2H, d, J = 8.3 Hz), 7.49 (1H, dd, J = 8.3 and 2.4 Hz), 6.65 (1H, d, J = 8.3 Hz), 4.40 (2H, t, J = 6.6 Hz), 3.84 (1H, dd, J = 7.6 and 4.7 Hz), 3.16 (3H, s), 2.90-2.82 (3H, m), 2.74 (1H, dd, J = 14.4 and 7.8 Hz), 2.29 (3H, s).	Calcd for $C_{22}H_{22}F_3N_2O_5$ 451.1476. Found: 451.1474	
D-10		^{1}H NMR (DMSO-d_6, 400 MHz) : 12.76 (1H, s), 7.96 (1H, d, J = 2.3 Hz), 7.79 (2H, d, J = 8.1), 7.55 (1H, dd, J = 8.6 and 2.5 Hz), 7.29 (2H, d, J = 8.1 Hz), 6.68 (1H, d, J = 8.3 Hz), 4.43 (2H, t, J = 6.8 Hz), 3.89 (1H, dd, J = 7.8 and 4.8 Hz), 3.22 (3H, s), 2.92-2.87 (3H, m), 2.80 (1H, dd, J = 14.2 and 7.8 Hz), 2.34 (3H, s), 2.30 (3H, s).	Calcd for $C_{22}H_{25}N_2O_6$ 397.1758. Found: 397.1770	Calcd for $C_{22}H_{24}N_2O_5$0.3$H_2$0 C 65.75 H 6.17 N 6.97. Found: C 65.74 H 6.14 N 6.81

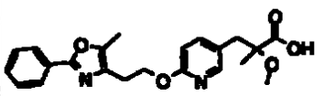
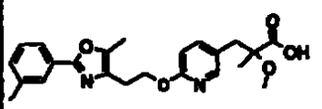
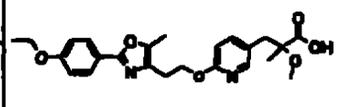
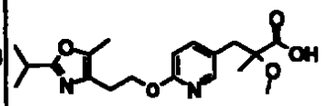
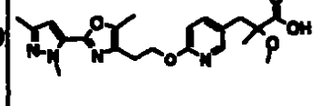
D-11		^{1}H NMR (MeOH-d_4, 400 MHz): 8.30 (1 H, s) 7.58 (1 H, d, J=9.2 Hz) 7.11 (2 H, d, J=8.2 Hz) 6.71 (2 H, d, J=8.2 Hz) 6.31 (1 H, d, J=9.2 Hz) 4.57 (2 H, t, J=6.5 Hz) 4.18 (1 H, dd, J=13.5, 0.2 Hz) 3.98 (2 H, q, J=7.7 Hz) 3.52 (3 H, s) 3.28 (2 H, t, J=6.5 Hz) 3.05 - 3.11 (1 H, m) 2.89 - 2.98 (1 H, m) 1.44 (3 H, t, J=7.7 Hz)	LRMS: 410 $(M+H)^+$.	
D-12		^{1}H NMR (MeOH-d_4, 400 MHz): 8.30 (1 H, s) 7.58 (1 H, d, J=9.2 Hz) 7.10 (2 H, d, J=8.2 Hz) 6.74 (2 H, d, J=8.2 Hz) 6.31 (1 H, d, J=9.2 Hz) 4.57 (2 H, t, J=6.5 Hz) 4.18 (1 H, dd, J=13.5, 0.2 Hz) 3.52 (3 H, s) 3.34 (3 H, s) 3.28 (2 H, t, J=6.5 Hz) 3.06 - 3.11 (1 H, m) 2.89 - 2.98 (1 H, m)	for LR 396 $(M+H)^+$	
D-13		^{1}H NMR (MeOH-d_4, 400 MHz): 8.30 (1 H, s) 7.58 (1 H, d, J=9.2 Hz) 7.31 - 7.37 (2 H, m, J=8.0, 7.5, 0.2, 0.2 Hz) 7.06 - 7.14 (3 H, m) 6.96 - 7.04 (4 H, m) 6.31 (1 H, d, J=9.2 Hz) 4.57 (2 H, t, J=6.5 Hz) 4.18 (1 H, dd, J=13.5, 0.2 Hz) 3.52 (3 H, s) 3.28 (2 H, t, J=6.5 Hz) 3.06 - 3.11 (1 H, m) 2.89 - 2.97 (1 H, m)	for LR 394 $(M+H)^+$	
D-14		^{1}H NMR (MeOH-d_4, 400 MHz): 8.28 - 8.34 (1 H, m) 7.59 (1 H, m) 7.31 - 7.37 (2 H, m) 6.96 - 7.14 (7 H, m) 6.27 - 6.34 (1 H, m) 4.53 - 4.60 (2 H, m) 4.22 - 4.30 (1 H, m) 3.49 - 3.66 (2 H, m) 3.25 - 3.31 (2 H, m) 3.05 - 3.11 (1 H, m) 2.89 - 2.97 (1 H, m) 1.19 (3 H, t, J=7.0 Hz)	LRMS: 409 $(M+H)^+$.	
D-15		^{1}H NMR (MeOH-d_4, 400 MHz): 8.31 (1 H, s) 8.02 (2 H, d, J=8.3 Hz) 7.59 (1 H, d, J=9.1 Hz) 7.43 (2 H, d, J=8.3 Hz) 6.31 (1 H, d, J=9.1 Hz) 4.20 - 4.29 (3 H, m) 3.49 - 3.66 (2 H, m) 3.05 - 3.11 (1 H, m) 2.89 - 2.97 (1 H, m) 2.70 (2 H, t, J=8.0 Hz) 2.19 (3 H, s) 1.19 (3 H, t, J=7.0 Hz)	for LR 432 $(M+H)^+$	

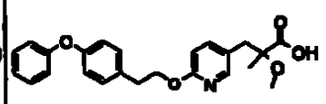
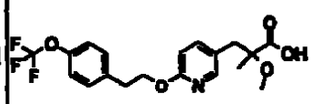
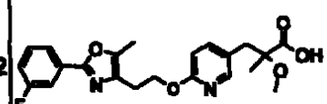
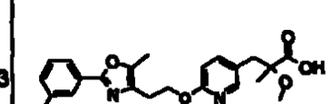
D-16		^{1}H NMR (MeOH-d_4, 400 MHz): 8.31 (1 H, s) 7.59 (1 H, d, J=9.1 Hz) 6.87 (2 H, d, J=8.2 Hz) 6.73 (2 H, d, J=8.2 Hz) 6.31 (1 H, d, J=9.2 Hz) 4.57 (2 H, t, J=6.5 Hz) 4.43 (2 H, s) 4.26 (1 H, dd, J=13.5, 0.2 Hz) 3.76 (2 H, s) 3.49 - 3.66 (2 H, m) 3.38 (3 H, s) 3.28 (2 H, t, J=6.5 Hz) 3.05 - 3.11 (1 H, m) 2.89 - 2.97 (1 H, m) 1.19 (3 H, t, J=7.0 Hz)	for LR 391 (M+H)$^+$	
D-17		^{1}H NMR (MeOH-d_4, 400 MHz): 8.31 (1 H, s) 7.86 - 7.74 (5 H, m) 7.59 (1 H, d, J=9.1 Hz) 7.19 (2 H, d, J=8.2 Hz) 6.86 (2 H, d, J=8.3 Hz) 6.31 (1 H, d, J=9.2 Hz) 4.57 (2 H, t, J=6.5 Hz) 4.26 (1 H, dd, J=13.5, 0.2 Hz) 3.49 - 3.66 (2 H, m) 3.28 (2 H, t, J=6.5 Hz) 3.05 - 3.11 (1 H, m) 2.89 - 2.97 (1 H, m) 1.19 (3 H, t, J=7.0 Hz)	for LR 473 (M+H)$^+$	
D-18		^{1}H NMR (MeOH-d_4, 400 MHz): 8.31 (1 H, s) 7.59 (1 H, d, J=9.1 Hz) 7.11 (2 H, d, J=8.2 Hz) 6.71 (2 H, d, J=8.2 Hz) 6.31 (1 H, d, J=9.2 Hz) 4.57 (2 H, t, J=6.5 Hz) 4.26 (1 H, dd, J=13.5, 0.2 Hz) 3.98 (2 H, q, J=7.7 Hz) 3.49 - 3.66 (2 H, m) 3.28 (2 H, t, J=6.5 Hz) 3.05 - 3.11 (1 H, m) 2.89 - 2.97 (1 H, m) 1.44 (3 H, t, J=7.7 Hz) 1.19 (3 H, t, J=7.0 Hz)	for LR 425 (M+H)$^+$	
D-19		^{1}H NMR (MeOH-d_4, 400 MHz): 8.31 (1 H, s) 7.59 (1 H, d, J=9.1 Hz) 7.10 (2 H, d, J=8.2 Hz) 6.74 (2 H, d, J=8.2 Hz) 6.31 (1 H, d, J=9.2 Hz) 4.57 (2 H, t, J=6.5 Hz) 4.26 (1 H, dd, J=13.5, 0.2 Hz) 3.49 - 3.66 (2 H, m) 3.34 (3 H, s) 3.28 (2 H, t, J=6.5 Hz) 3.05 - 3.11 (1 H, m) 2.89 - 2.97 (1 H, m) 1.19 (3 H, t, J=7.0 Hz)	for LR 411 (M+H)$^+$	
D-20		^{1}H NMR (MeOH-d_4, 400 MHz): 8.31 (1 H, s) 7.59 (1 H, d, J=9.1 Hz) 7.34 (2 H, d, J=8.2 Hz) 7.24 (2 H, d, J=8.2 Hz) 6.31 (1 H, d, J=9.2 Hz) 4.57 (2 H, t, J=6.5 Hz) 4.26 (1 H, dd, J=13.5, 0.2 Hz) 3.49 - 3.66 (2 H, m) 3.28 (2 H, t, J=6.5 Hz) 3.05 - 3.11 (1 H, m) 2.89 - 2.97 (1 H, m) 1.19 (3 H, t, J=7.0 Hz)	for LR 400 (M+H)$^+$	

				
D-21		^{1}H NMR (MeOH-d_4, 400 MHz): 8.31 (1 H, s) 7.59 (1 H, d, J=9.1 Hz) 6.94 (2 H, d, J=8.2 Hz) 6.66 (2 H, d, J=8.3 Hz) 6.31 (1 H, d, J=9.2 Hz) 4.57 (2 H, t, J=6.5 Hz) 4.26 (1 H, dd, J=13.5, 0.2 Hz) 4.01 (2 H, q, J=6.9 Hz) 3.49 - 3.66 (2 H, m) 3.28 (2 H, t, J=6.5 Hz) 3.05 - 3.11 (1 H, m) 2.89 - 2.97 (1 H, m) 1.40 (3 H, t, J=7.0 Hz) 1.19 (3 H, t, J=7.0 Hz)	for LR 360 (M+H)$^+$	
D-22		^{1}H NMR (MeOH-d_4, 400 MHz): 8.31 (1 H, s) 7.59 (1 H, d, J=9.1 Hz) 6.97 (2 H, d, J=8.2 Hz) 6.77 (2 H, d, J=8.2 Hz) 6.31 (1 H, d, J=9.2 Hz) 4.57 (2 H, t, J=6.5 Hz) 4.26 (1 H, dd, J=13.5, 0.2 Hz) 3.78 (3 H, s) 3.49 - 3.66 (2 H, m) 3.28 (2 H, t, J=6.5 Hz) 3.05 - 3.11 (1 H, m) 2.89 - 2.97 (1 H, m) 1.19 (3 H, t, J=7.0 Hz)	for LR 346 (M+H)$^+$	
D-23		(MeOD, 400 MHz): 8.03 (1H, d, J = 2.8 Hz), 7.84-7.82 (2H, m), 7.35-7.34 (3H, m), 7.26 (1H, dd, J = 8.6, 2.5 Hz), 7.16 (1H, d, J = 8.6 Hz), 4.20 (2H, t, J = 6.4 Hz), 4.06 (1H, dd, J = 8.6, 4.6 Hz), 3.52-3.44 (1H, m), 3.22-3.14 (1H, m), 3.03 (1H, dd, J = 13.9, 4.6 Hz), 2.88 (2H, t, J = 6.3 Hz), 2.82 (1H, d, J = 9.1 Hz), 2.26 (3H, s), 0.94 (3H, t, J = 7.0 Hz)	for LR 397 (M+H)$^+$	

D-24		($CDCl_3$, 400 MHz): 8.25 (1H, d, J = 1.5 Hz), 7.95 (2H, dd, J = 7.8, 1.8 Hz), 7.44-7.36 (3H, m), 7.28-7.22 (2H, m), 4.19 (1H, dd, J = 7.1, 4.8 Hz), 4.02 (2H, t, J = 6.1 Hz), 3.80-3.72 (1H, m), 3.47-3.39 (1H, m), 3.34 (1H, dd, J = 15.2, 7.1 Hz), 3.20 (1H, dd, J = 15.2, 4.3 Hz), 2.67 (2H, t, J = 7.2 Hz), 2.27 (3H, s), 2.18-2.12 (2H, m), 1.17 (3H, t, J = 7.0 Hz)	for LR 411 $(M+H)^+$	
D-25		($CDCl_3$, 400 MHz): 8.16 (1H, d, J = 2.3 Hz), 7.24-7.19 (2H, m), 4.27 (2H, t, J = 6.8 Hz), 4.17 (1H, dd, J = 7.6, 3.8 Hz), 3.79-3.72 (1H, m), 3.47-3.40 (1H, m), 3.32 (1H, dd, J = 15.4, 7.6 Hz), 3.18 (1H, dd, J = 15.4, 3.5 Hz), 3.09 (2H, t, J = 6.7 Hz), 2.59 (3H, s), 2.34 (3H, s), 1.17 (3H, t, J = 7.0 Hz)	for LR 351 $(M+H)^+$	
D-26		(MeOD, 400 MHz): 8.01 (1H, d, J = 3.0 Hz), 7.74-7.71 (2H, m), 7.34-7.27 (3H, m), 7.24 (1H, dd, J = 8.8, 2.8 Hz), 7.14 (1H, d, J = 8.8 Hz), 4.27 (2H, t, J = 6.8 Hz), 4.06 (1H, dd, J = 8.7, 4.7 Hz), 3.51-3.44 (1H, m), 3.22-3.14 (1H, m), 3.08 (2H, t, J = 6.4 Hz), 3.02 (1H, dd, J = 14.2, 4.6 Hz), 2.89 (1H, dd, J = 13.9, 8.8 Hz), 2.34 (3H, s), 0.93 (3H, t, J = 7.1 Hz)	for LR 413 $(M+H)^+$	
D-27		(MeOD, 400 MHz): 7.86-7.82 (3H, m), 7.47 (1H, dd, J = 8.8, 2.0 Hz), 7.39-7.36 (3H, m), 6.62 (1H, d, J = 8.3 Hz), 4.14 (2H, t, J = 6.2 Hz), 3.22-3.20 (3H, m), 2.85 (2H, dd, J = 22.5, 13.9 Hz), 2.60 (2H, t, J = 7.1 Hz), 2.19 (3H, s), 2.03 (2H, dd, J = 12.9, 6.1 Hz), 1.26 (3H, s)	for LR 411 $(M+H)^+$	
D-28		(MeOD, 400 MHz): 8.02 (1H, d, J = 2.5 Hz), 7.85-7.83 (2H, m), 7.39-7.33 (3H, m), 7.26 (1H, dd, J = 8.8, 2.8 Hz), 7.20 (1H, d, J = 8.8 Hz), 3.96 (2H, t, J = 6.1 Hz), 3.20 (3H, s), 3.05 (2H, dd, J = 21.0, 13.9 Hz), 2.61 (2H, t, J = 7.2 Hz), 2.20 (3H, s), 2.07-2.01 (2H, m), 1.24 (3H, s)	for LR 411 $(M+H)^+$	

D-29		(MeOD, 400 MHz): 8.02 (1H, d, *J* = 2.8 Hz), 7.87-7.83 (2H, m), 7.39-7.36 (3H, m), 7.27 (1H, dd, *J* = 8.6, 2.8 Hz), 7.19 (1H, d, *J* = 8.6 Hz), 4.22 (2H, t, *J* = 6.4 Hz), 3.19 (3H, s), 3.05 (2H, dd, *J* = 21.2, 13.9 Hz), 2.91 (2H, t, *J* = 6.4 Hz), 2.29 (3H, s), 1.23 (3H, s)	for LR 397 (M+H)+	
D-30		(MeOD, 400 MHz): 7.87-7.84 (3H, m), 7.48 (1H, dd, *J* = 8.6, 2.3 Hz), 7.41 (2H, d, *J* = 8.6 Hz), 6.61 (1H, d, *J* = 8.6 Hz), 4.42 (2H, t, *J* = 6.6 Hz), 3.22 (3H, s), 2.91-2.88 (3H, m), 2.83 (1H, d, *J* = 13.9 Hz), 2.27 (3H, s), 1.25 (3H, s)	for LR 431 (M+H)+	
D-31		(MeOD, 400 MHz): 8.04 (2H, d, *J* = 8.1 Hz), 7.84 (1H, d, *J* = 2.0 Hz), 7.70 (2H, d, *J* = 8.3 Hz), 7.48 (1H, dd, *J* = 8.5, 2.4 Hz), 6.60 (1H, d, *J* = 8.3 Hz), 4.43 (2H, t, *J* = 6.6 Hz), 3.22 (3H, s), 2.91 (2H, t, *J* = 6.4 Hz), 2.88 (1H, d, *J* = 14.2 Hz), 2.82 (1H, d, *J* = 14.2 Hz), 2.28 (3H, s), 1.25 (3H, s)	for LR 465 (M+H)+	
D-32		(MeOD, 400 MHz): 7.84 (1H, d, *J* = 2.0 Hz), 7.47 (1H, dd, *J* = 8.5, 2.4 Hz), 6.59 (1H, d, *J* = 8.6 Hz), 4.32 (2H, t, *J* = 6.6 Hz), 3.23 (3H, s), 2.89 (1H, d, *J* = 14.2 Hz), 2.83 (1H, d, *J* = 13.9 Hz), 2.78 (2H, t, *J* = 6.7 Hz), 2.64 (1H, tt, *J* = 11.6, 3.5 Hz), 2.13 (3H, s), 1.93-1.89 (2H, m), 1.75-1.71 (2H, m), 1.65-1.62 (1H, m), 1.50-1.40 (2H, m), 1.37-1.27 (2H, m), 1.26 (3H, s), 1.23-1.19 (1H, m)	for LR 403 (M+H)+	
D-33		(MeOD, 400 MHz): 7.85 (1H, d, *J* = 2.3 Hz), 7.77 (2H, dd, *J* = 7.6, 1.8 Hz), 7.47 (1H, dd, *J* = 8.5, 2.3 Hz), 7.39-7.31 (3H, m), 6.61 (1H, d, *J* = 8.6 Hz), 4.49 (2H, t, *J* = 6.7 Hz), 3.23 (3H, s), 3.11 (2H, t, *J* = 6.7 Hz), 2.89 (1H, d, *J* = 13.9 Hz), 2.83 (1H, d, *J* = 14.2 Hz), 2.36 (3H, s), 1.26 (3H, s)	for LR 413 (M+H)+	
D-34		(MeOD, 400 MHz): 7.84 (1H, d, *J* = 2.3 Hz), 7.43 (1H, dd, *J* = 8.5, 2.4 Hz), 7.17 (2H, dd, *J* = 8.1, 0.8 Hz), 7.09-7.05 (1H, m), 6.94 (1H, dt, *J* = 7.8, 1.0 Hz), 6.53 (1H, d, *J* = 8.3 Hz), 4.49 (2H, t, *J* = 5.3 Hz), 3.87 (2H, t, *J* = 5.3 Hz), 3.23 (3H, s), 3.18	for LR 386 (M+H)+	

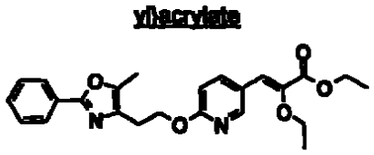
		(3H, s), 2.88 (1H, d, *J* = 13.9 Hz), 2.82 (1H, d, *J* = 13.9 Hz), 1.26 (3H, s)		
D-35		(Dimethyl sulfoxide-d_6, 300 MHz): 7.91 (3H, m), 7.49 (4H, m), 7.40 (3H, m), 6.69 (1H, d, *J* = 8.5 Hz), 4.44 (2H, t, *J* = 6.7 Hz), 3.44 (2H, m), 3.18 (3H, s), 2.89 (2H, m), 2.31 (3H, s), 1.19 (3H, s)	for LR 395 (M)$^-$	Calcd $C_{22}H_{24}N_2O_5$ C 66.65, H 6.10, N 7.07. Found: $C_{22}H_{24}N_2O_5 \cdot 0.06H_2O$ C 66.16, H 6.15, N 6.96.
D-36		(MeOD, 400 MHz): 7.83 (1H, d, *J* = 1.8 Hz), 7.69 (1H, s), 7.65 (1H, d, *J* = 7.6 Hz), 7.46 (1H, dd, *J* = 8.6, 2.3 Hz), 7.25 (1H, t, *J* = 7.6 Hz), 7.19 (1H, d, *J* = 7.6 Hz), 6.59 (1H, d, *J* = 8.3 Hz), 4.39 (2H, t, *J* = 6.6 Hz), 3.19 (3H, s), 2.87 (2H, t, *J* = 6.4 Hz), 2.87 (1H, d, *J* = 13.9 Hz), 2.80 (1H, d, *J* = 13.9 Hz), 2.30 (3H, s), 2.24 (3H, s), 1.21 (3H, s)	for LR 411 (M+H)$^+$	
D-37		(MeOD, 400 MHz): 7.83 (1H, d, *J* = 2.3 Hz), 7.79-7.76 (2H, m), 7.46 (1H, dd, *J* = 8.5, 2.4 Hz), 6.90 (2H, d, *J* = 8.8 Hz), 6.59 (1H, d, *J* = 8.6 Hz),4.38 (2H, t, *J* = 6.7 Hz), 4.00 (2H, q, *J* = 7.1 Hz), 3.21 (3H, s), 2.88 (1H, d, *J* = 13.9 Hz), 2.86 (2H, t, *J* = 6.6 Hz), 2.81 (1H, d, *J* = 13.9 Hz), 2.22 (3H, s), 1.31 (3H, t, *J* = 7.0 Hz), 1.24 (3H, s)	for LR 441 (M+H)$^+$	
D-38		($CDCl_3$, 400 MHz): 7.93 (1H, d, *J* = 2.3 Hz), 7.45 (1H, dd, *J* = 8.5, 2.4 Hz), 6.63 (1H, d, *J* = 8.6 Hz), 4.40 (2H, t, *J* = 6.8 Hz), 3.37 (3H, s), 3.05-2.96 (1H, m), 2.97 (1H, d, *J* = 14.4 Hz), 2.92 (1H, d, *J* = 14.4 Hz), 2.88 (2H, t, *J* = 6.7 Hz), 2.20 (3H, s), 1.43 (3H, s), 1.30 (3H, s), 1.28 (3H, s)	for LR 383 (M+H)$^+$	
D-39		(MeOD, 400 MHz): 7.82 (1H, d, *J* = 2.0 Hz), 7.44 (1H, dd, *J* = 8.6, 2.3 Hz), 6.57 (1H, d, *J* = 8.6 Hz), 6.45 (1H, s), 4.39 (2H, t, *J* = 6.4 Hz), 4.00 (3H, s), 3.20 (3H, s), 2.86 (2H, t, *J* = 6.6 Hz), 2.86 (1H, d, *J* = 14.2 Hz), 2.80 (1H, d, *J* = 14.2 Hz), 2.22 (3H, s), 2.14 (3H, s), 1.23 (3H, s)	for LR 415 (M+H)$^+$	

D-40		(MeOD, 400 MHz): 7.82 (1H, d, *J* = 2.3 Hz), 7.44 (1H, dd, *J* = 8.0, 1.9 Hz), 7.34-7.29 (2H, m), 7.22 (2H, d, *J* = 8.6 Hz), 7.09-7.03 (1H, m), 6.96-6.91 (4H, m), 6.80 (1H, d, *J* = 8.6 Hz), 4.33 (2H, t, *J* = 7.1 Hz), 3.20 (3H, s), 3.00 (2H, t, *J* = 7.0 Hz), 2.82 (1H, d, *J* = 14.2 Hz), 2.80 (1H, d, *J* = 14.2 Hz), 1.23 (3H, s)	for LR 408 $(M+H)^+$	
D-41		(MeOD, 400 MHz): 7.81 (1H, d, *J* = 2.3 Hz), 7.44 (1H, dd, *J* = 8.6, 2.3 Hz), 7.27 (2H, d, *J* = 8.6 Hz), 7.07 (2H, d, *J* = 7.8 Hz), 6.57 (1H, d, *J* = 8.6 Hz), 4.33 (2H, t, *J* = 6.7 Hz), 3.20 (3H, s), 2.97 (2H, t, *J* = 6.7 Hz), 2.84 (1H, d, *J* = 14.2 Hz), 2.82 (1H, d, *J* = 14.2 Hz), 1.24 (3H, s)	for LR 400 $(M+H)^+$	
D-42		(MeOD, 400 MHz): 7.83 (1H, d, *J* = 1.8 Hz), 7.65 (1H, d, *J* = 7.6 Hz), 7.46 (1H, dd, *J* = 8.6, 2.3 Hz), 7.29 (1H, s), 7.25 (1H, t, *J* = 7.8 Hz), 7.19 (1H, d, *J* = 7.8 Hz), 6.59 (1H, d, *J* = 8.3 Hz), 4.39 (2H, t, *J* = 6.6 Hz), 3.19 (3H, s), 2.87 (2H, t, *J* = 6.4 Hz), 2.87 (1H, d, *J* = 13.9 Hz), 2.80 (1H, d, *J* = 13.9 Hz), 2.24 (3H, s), 1.21 (3H, s)	for LR 415 $(M+H)^+$	
D-43		(MeOD, 400 MHz): 7.81 (1H, d, *J* = 2.3 Hz), 7.45-7.38 (2H, m), 7.32-7.24 (2H, m), 6.91 (1H, dd, *J* = 8.0, 2.4 Hz), 6.58 (1H, d, J = 8.3 Hz), 4.38 (2H, t, *J* = 6.7 Hz), 3.74 (3H, s), 3.18 (3H, s), 2.86 (2H, t, *J* = 6.7 Hz), 2.85 (1H, d, *J* = 13.9 Hz), 2.79 (1H, d, *J* = 13.9 Hz), 2.22 (3H, s), 1.22 (3H, s)	for LR 427 $(M+H)^+$	

Preparations of starting materials for Examples D-1 to D-43 (Preparations d-1 to d-42):

Preparation d-1

Ethyl 2-ethoxy-3-[6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridin-3-yl]acrylate



N,N,N',N'-tetramethylguanidine (0.305 mL, 2.43 mmol) was added dropwise to a solution of 6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]nicotinaldehyde (250 mg,

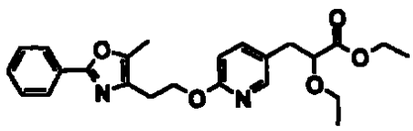
0.811 mmol) and (1,2-diethoxy-2- oxoethyl)(triphenyl)phosphonium chloride (686 mg, 1.62 mmol) in chloroform (4 mL). The mixture was stirred for 16 hours then partitioned between saturated ammonium chloride solution and ethyl acetate. The organic phase was washed with brine, dried over magnesium sulfate, filtered and evaporated* and evaporated. The residue was purified by flash column chromatography (1:2 ethyl acetate:hexanes) to yield the title compound as a white solid (330 g, 96%).

LRMS (*m/z*): 423 $(M+H)^+$.

^{1}H NMR ($CDCl_3$, 300 MHz) 8.42 (1H, m), 8.10 (1H, m), 7.97 (1H, m), 7.40 (2H, m), 7.28 (3H, m), 6.90 (1H, s), 6.73 (1H, m), 4.60 (2H, t, *J* = 7 Hz), 4.30 (2H, q, *J* = 7 Hz), 4.01 (2H, q, *J* = 7 Hz), 2.99 (2H, t, *J* = 7 Hz), 2.34 (3H, s), 1.36 (6H, m)

Preparation d-2

Ethyl 2-ethoxy-3-(6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridin-3-yl)propanoate



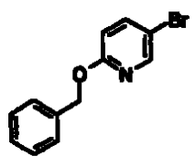
A solution of ethyl 2-ethoxy-3-(6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridin-3-yl)acrylate (326 mg, 0.776 mmol) in ethanol (10 mL) was hydrogenated at 50psi over 10% palladium on carbon (33 mg) for 3 hours. The mixture was filtered through celite and the solid was washed with ethyl acetate. The filtrate and washings were evaporated and the residue was purified by flash column chromatography (1:2 ethyl acetate:hexanes) to yield the title compound as a colorless oil (183 mg, 56%).

LRMS (*m/z*): 425 $(M+H)^+$.

^{1}H NMR ($CDCl_3$, 300 MHz) 7.99 (3H, m), 7.42 (4H, m), 6.85 (1H, m), 4.54 (2H, t, *J* = 7 Hz), 4.18 (2H, q, *J* = 7 Hz), 3.93 (1H, m), 3.63 (1H, m), 3.36 (1H, m), 2.90 (4H, m), 2.33 (3H, s), 1.25 (3H, t, *J* = 7 Hz), 1.16 (3H, t, *J* = 7 Hz).

Preparation d-3

Preparation of 2-(benzyloxy)-5-bromopyridine



To a solution of 5-bromopyridin-2(1*H*)-one (100 mmol, 17.4 g, 1.0 eq.) in benzene (170 mL) was added silver (I) carbonate (67.0 mmol, 18.5 g, 0.67 eq.). The flask was wrapped with aluminum foil and then benzyl bromide (120 mmol, 20.5 g, 1.2 eq.) was added via syringe in a steady stream. The mixture was heated to 50 °C

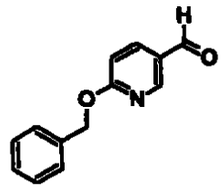
and stirred in the dark for approximately 24 hours. LC/MS of the reaction mixture indicates two peaks both with M+H = 265 corresponding to the desired molecular weight. On the basis of relative polarities, the more polar peak was thought to be the N-alkylated product and consisted of approximately 20 % of the total. The reaction mixture was allowed to cool to room temperature and the silver salt was removed by filtration of the mixture through a pad of celite. The filter cake was washed with benzene and the organic layer was washed twice with 2% sodium bicarbonate and twice with water. The organic layer was dried over magnesium sulfate and concentrated *in vacuo*. The crude residue was purified on a Biotage Sp4 65i over a gradient of 5-95% hexanes in ethyl acetate to afford the title compound as a golden oil (25.1 g, 95%).

LRMS: 265 $(M+H)^+$.

^{1}H NMR (DMSO-d_6, 400 MHz); 8.29 (1 H, s) 7.72 (1 H, d, J=8.5 Hz) 7.31 - 7.43 (5 H, m) 6.54 (1 H, d, J=8.5 Hz) 5.34 (2 H, s)

Preparation d-4

Preparation of 6-(benzyloxy)nicotinaldehyde



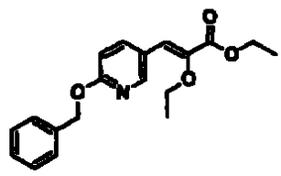
n-Butyl lithium (2.5M, 95.9 mmol, 38.4 mL, 1.05 eq.) was added dropwise via syringe to a stirred solution of 2-(benzyloxy)-5-bromopyridine (91.3 mmol, 24.1 g, 1.0 eq.) in THF (260 mL, c = 0.35) cooled to –78 °C. Upon completion of addition, the solution was allowed to continue stirring at the same low temperature for 1 hour. At this point, *N,N*-dimethylformamide (183 mmol, 13.4 g, 2.0 eq.) was added dropwise as a solution in 5 mL THF. Stirring was continued at the same low temperature for a further 30 minutes at which point the reaction was quenched by addition of 5% sodium bicarbonate. The mixture was transferred to a separatory funnel and extracted with ether (3 x 250 mL). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The resultant yellow oil was purified on a Biotage Sp4 65i over a gradient of 0 – 50% hexanes in ethyl acetate to afford the title compound (14.1 g, 73%).

LRMS: 214 $(M+H)^+$.

^{1}H NMR (DMSO-d_6, 400 MHz); 10.02 (1 H, s) 8.66 (1 H, s) 8.03 (1 H, d, J=9.3 Hz) 7.31 - 7.43 (5 H, m) 6.50 (1 H, d, J=9.3 Hz) 5.33 (2 H, s)

Preparation d-5

Preparation of ethyl (2Z)-3-[6-(benzyloxy)pyridin-3-yl]-2-ethoxyacrylate



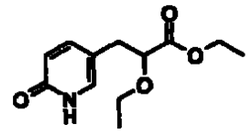
To a solution of 6-(benzyloxy)nicotinaldehyde (1.0 eq., 33.1 mmol, 7.05 g) and (1,2-diethoxy-2-oxoethyl)(triphenyl)phosphonium chloride (2.0 eq., 66.2 mmol, 28.4 g) in chloroform (165 mL, 0.2 M) was added tetramethylguanidine (3.0 eq., 99.3 mmol, 11.4 g). The flask was capped with a hollow glass stopper and stirred at room temperature overnight. TLC analysis after approximately 18 hours indicated the presence of a small amount of unreacted starting material. The reaction mixture was heated to reflux and TLC reanalyzed after 2 hours. The reaction was quenched with saturated ammonium chloride. The layers were separated and the organic layer was washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. A large amount of triphenylphosphine oxide precipitated. The residue was triturated with ether and filtered. Washed filter cake with ether and concentrated combined filtrates *in vacuo* to afford a pale yellow solid which was dissolved in a minimal amount of DCM and loaded onto Biotage Sp4 65i and eluted over a gradient of 10 – 100 % hexanes to ethyl acetate. Obtained 12.3 g of a clear, colorless oil (37.6 mmol, quant.).

LRMS: 328 $(M+H)^+$.

^{1}H NMR (DMSO-d_6, 400 MHz): 8.33 (1 H, s) 7.92 (1 H, d, J=8.0 Hz) 7.31 - 7.43 (6 H, m) 6.76 (1 H, d, J=8.1 Hz) 6.60 (1 H, s) 5.37 (2 H, s) 4.23 (2 H, q, J=7.1 Hz) 3.90 - 3.99 (2 H, m) 1.34 (6 H, dt, J=15.8, 7.0 Hz)

Preparation d-8

Preparation of ethyl 2-ethoxy-3-(6-oxo-1,6-dihydropyridin-3-yl)propanoate

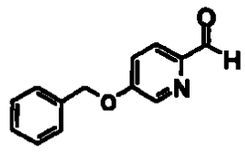


To a Parr shaker bottle containing a solution of ethyl (2Z)-3-[6-(benzyloxy)pyridin-3-yl]-2-ethoxyacrylate in ethanol was added 10% Pd on carbon (~ 1.23 g). The bottle was purged with hydrogen and degassed under reduced pressure three times. The mixture was placed under 50 psi hydrogen and shaken at room temperature overnight. After ~ 20 hours shaking was stopped and the bottle was degassed in vacuo. TLC analysis indicated consumption of starting material. The mixture was filtered through a pad of celite to remove palladium. The filter cake was washed with an additional portion of ethanol. This solution was concentrated *in vacuo* to yield the reduced and debenzylated pyridone as a golden oil. This oil

was purified on a Biotage Sp4, 65i, 80 mL/min over a gradient of 0 – 10% MeOH in DCM to yield 2.77 g of a clear, colorless oil (11.6 mmol, 31%).
LRMS: 240 $(M+H)^+$.
^{1}H NMR (DMSO-d_6, 400 MHz): 7.29 (1 H, d, J=9.5 Hz) 7.19 (1 H, d, J=6.2 Hz) 6.55 (1 H, d, J=9.5 Hz) 4.20 (2 H, q, J=7.0 Hz) 4.10 (1 H, dd, J=9.6, 0.3 Hz) 3.59 - 3.73 (2 H, m) 2.65 - 2.70 (1 H, m) 2.53 - 2.61 (1 H, m) 1.23 (6 H, td, J=7.0, 3.6 Hz)

Preparation d-7

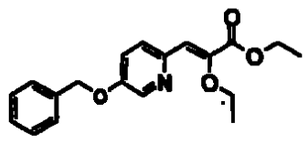
5-Benzyloxy-pyridine-2-carbaldehyde



To a solution of (5-benzyloxy-pyridin-2-yl)-methanol (2.3619 g, 10.9728 mmol) in dichloromethane (120 mL) and pyridine (2.68 mL, 32.9184 mmol) was added 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one (6.9812 g, 16.4592 mmol). The resulting solution was stirred, under an atmosphere of nitrogen at ambient temperature, for 16 hours and then diluted with diethyl ether (100 mL) followed by partial concentration under reduced pressure. The residue was taken up in diethyl ether (150 mL), and precipitates were removed by extraction with 1:1 10% aqueous sodium thiosulfate:saturated aqueous sodium bicarbonate (2 x 100 mL). The organic layer was washed with water (100 mL) and saturated aqueous sodium chloride (100 mL), dried (anhydrous magnesium sulfate), filtered, and concentrated *in vacuo* to afford the pure title compound (1.1694 g, 50%) as a pale yellow oil.
LRMS (*m/z*): 214 $(M+H)^+$.
^{1}H NMR ($CDCl_3$, 300 MHz): 9.96 (1H, d, *J* = 0.8 Hz), 8.49 (1H, d, *J* = 2.5 Hz), 7.94 (1H, d, J = 8.7 Hz), 7.44-7.40 (4H, m), 7.38-7.33 (2H, m), 5.19 (2H, s).

Preparation d-8

3-(5-Benzyloxy-pyridin-2-yl)-2-ethoxy-acrylic acid ethyl ester



To a solution of 5-benzyloxy-pyridine-2-carbaldehyde (1.1694 g, 5.4842 mmol), (ethoxycarbonyl-methoxy-methyl)-triphenyl-phosphonium chloride (4.7043 g, 10.9684 mmol) in chloroform (30 mL), under an atmosphere of nitrogen at ambient temperature, was added tetramethylguanidine (2.1 mL, 16.4526 mmol) dropwise. The resulting solution was stirred for 16 hours and then quenched with saturated aqueous ammonium chloride (50 mL). The phases were separated and the organic phase washed with saturated aqueous sodium chloride (50 mL), dried

(anhydrous magnesium sulfate), filtered and concentrated *in vacuo* to afford the crude product. The residue was purified by flash column chromatography (hexanes to ethyl acetate) to yield the pure title compound (1.8051 g, 100%) as a yellow oil.

LRMS (*m/z*): 328 $(M+H)^+$.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.37 (1H, d, *J* = 2.8 Hz), 8.18 (1H, d, *J* = 8.9 Hz), 7.44-7.33 (5H, m), 7.25 (1H, dd, *J* = 8.9, 3.0 Hz), 7.13 (1H, s), 5.13 (2H, s), 4.27 (2H, q, *J* = 7.2 Hz), 4.05 (2H, q, *J* = 7.2 Hz), 1.35 (3H, t, *J* = 7.0 Hz), 1.34 (3H, t, *J* = 7.0 Hz).

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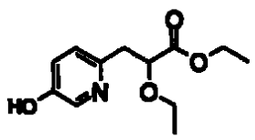
Preparation d-9

2-Ethoxy-3-(5-hydroxy-pyridin-2-yl)-propionic acid ethyl ester



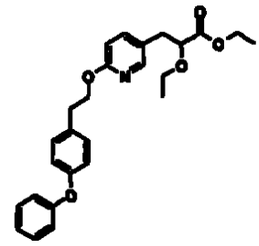
To a solution of 3-(5-benzyloxy-pyridin-2-yl)-2-ethoxy-acrylic acid ethyl ester (1.8051 g, 5.5144 mmol) in dry ethanol (40 mL) was added palladium (0.1805 g, 10 wt. % on activated carbon). The resulting solution was stirred at ambient temperature under an atmosphere of hydrogen (50psi) for 16 hours. The resulting solution was filtered through a 3" bed of Celite and washed with ethanol (200 mL). The filtrate was then concentrated *in vacuo* to afford the pure title compound (1.2231 g, 93%) as a pale yellow oil.

LRMS (*m/z*): 240 $(M+H)^+$.

^{1}H NMR ($CDCl_3$, 300 MHz): 8.14 (1H, s), 7.20-7.11 (2H, m), 4.19-4.10 (3H, m), 3.71 (1H, q, *J* = 7.0 Hz), 3.63-3.53 (1H, m), 3.36-3.26 (1H, m), 3.18-3.03 (1H, m), 1.18 (3H, t, *J* = 7.2 Hz), 1.07 (3H, t, *J* = 7.1 Hz).

Preparation d-10

ethyl 2-ethoxy-3-[6-[2-(4-phenoxyphenyl)ethoxy]pyridin-3-yl]propanoate

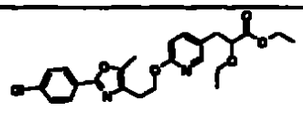
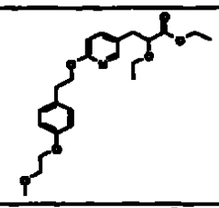
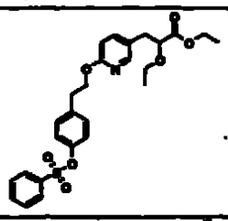
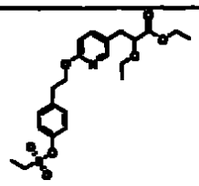
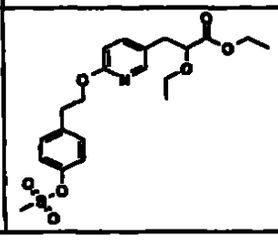


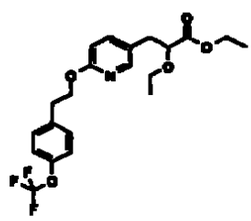
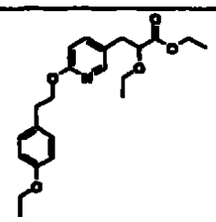
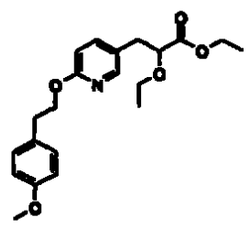
To an argon-purged solution of the appropriate bromopyridine (0.636 mmol) in toluene (12 mL) was added palladium (II) acetate (11.4 mg, 0.0508 mmol) and racemic-2-(Di-t-butylphosphino)-1,1'-binaphthyl (25.4 mg, 0.0636 mmol). The activated complex was allowed to form over approximately ten minutes, at which point cesium carbonate (414 mg, 1.27 mmol) and the appropriate alcohol (0.956

mmol) were added. The mixture was heated to 115 °C and stirred at this temperature for approximately 12-18 hours. The mixture was cooled to room temperature and filtered through a pad of silica. The filter pad was washed with 2-3 aliquots of ethyl acetate and the combined organic filtrates were combined and concentrated *in vacuo*. The resulting residue was either purified by flash chromatography, or subjected to the general hydrolysis procedure.

Preparations d-11 to d-18

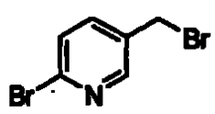
Preparations d-11 to d-18 were prepared by procedures analogous to those used for Preparation d-10

Prep #	Structure	^{1}H NMR	MS (*m/z*) (LR or HR)
d-11			
d-12			
d-13			
d-14			
d-15			

d-16			
d-17			
d-18			

Preparation d-19

2-Bromo-5-(bromomethyl)pyridine



Phosphorous tribromide (100 mmol, 27.1 g, 2.0 eq.) was added carefully to 2-chloro-5-hydroxymethyl pyridine (50.0 mmol, 7.18 g, 1.0 eq.). The pyridine clumped together and the mixture was heated to 160 °C. Within 5 minutes of stirring at >150 °C the mixture went very dark in color with gas evolution. The mixture was stirred at this same temperature for approximately 2.5 hours at which point it was cooled to room temperature. The mixture was cooled further to 0 °C whereupon saturated sodium bicarbonate was added very cautiously (highly exothermic!). As foaming became less vigorous, ice was added to the mixture until foaming subsided. Solid sodium bicarbonate was then carefully added to achieve a pH of ~ 8-9. The mixture was extracted with ethyl acetate and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. Concentrated in vacuo to afford a dark solid. This material was dissolved in a

8/8
89

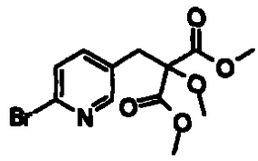
minimal amount of DCM and purified using a Biotage Sp4 65i over a gradient of 0 – 100 % ethyl acetate in hexanes to afford the title compound as a pale yellow solid (5.57 g, 44%).

LRMS: 252 $(M+H)^+$.

^{1}H NMR (DMSO-d_6, 400 MHz); 8.39 (1H, s) 7.59 (1H, d, *J* = 8.5 Hz) 7.48 (1H, d, *J* = 8.5 Hz) 4.46 (2H, s)

Preparation d-20

Preparation of dimethyl [(6-bromopyridin-3-yl)methyl](methoxy)malonate



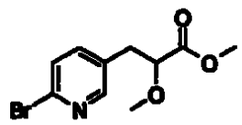
To a slurry of potassium *t*-butoxide (46.6 mmol, 5.22 g, 1.3 eq.) in anhydrous DMF (250 mL) cooled to 0 °C was added methoxy dimethylmalonate (46.6 mmol, 7.55 g, 1.3 eq.) via syringe in small portions. The enolate was allowed to form over approximately 30 minutes at which point 2-bromo-5-(bromomethyl)pyridine was added portionwise. The reaction mixture was allowed to warm slowly to room temperature over 3 hours. The reaction mixture was diluted with ethyl ether and transferred to a separatory funnel containing saturated ammonium chloride. The layers were shaken and separated and the organic layer was washed with water. The organic layer was then dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The yellow oil obtained was purified on a Biotage Sp4 65i over a gradient of 0 – 100 % ethyl acetate in hexanes to afford a colorless oil that solidified on standing (12.1 g, quant.)

LRMS: 333 $(M+H)^+$.

^{1}H NMR (DMSO-d_6, 400 MHz); 8.27 (1 H, s) 7.45 - 7.55 (2 H, m) 3.82 (6 H, s) 3.57 (3 H, s) 3.42 (2 H, s)

Preparation d-21

Preparation of methyl 3-(6-bromopyridin-3-yl)-2-methoxypropanoate



To a solution of dimethyl [(6-bromopyridin-3-yl)methyl](methoxy)malonate (3.55 mmol, 1.18 g, 1.0 eq.) in anhydrous DMF (2 mL) was added lithium bromide (3.20 mmol, 0.278 g, 0.9 eq.) followed by water (3.55 mmol, 0.064 g, 1.0 eq.). The solution was placed in a oil bath preheated to 165 °C. Rapid gas evolution commenced. Bubble formation ceased within 30 minutes and LC/MS of the reaction mixture at this time indicated reaction was complete. Cooled to room

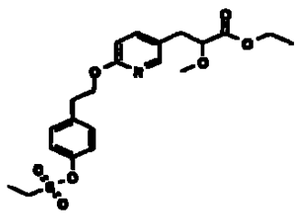
temperature and diluted with water. Extracted aqueous layer with ethyl ether (4x 25 mL). Combined organic layers and washed with brine. Dried organic layer over anhydrous magnesium sulfate and concentrated *in vacuo* to afford 536 mg of a brown oil that was a single spot by TLC. Used in next step without further purification.

LRMS: 275 $(M+H)^+$.

^{1}H NMR (DMSO-d_6, 400 MHz); 8.23 (1 H, s) 7.42 - 7.51 (2 H, m) 4.28 (1 H, d, J=8.1 Hz) 3.79 (3 H, s) 3.51 (3 H, s) 2.97 - 3.03 (1 H, m) 2.82 - 2.88 (1 H, m).

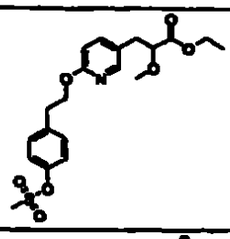
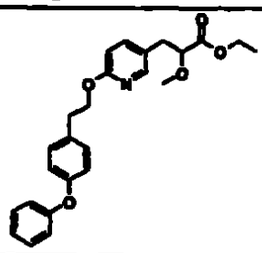
Preparation d-22

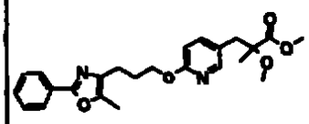
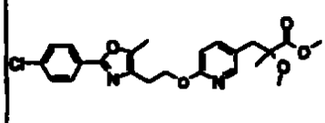
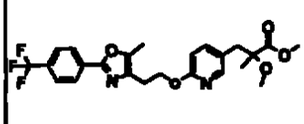
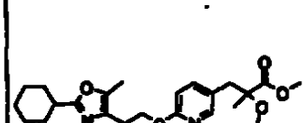
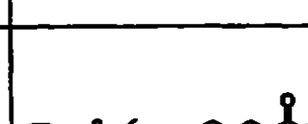
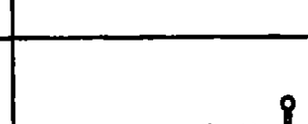
ethyl 3-[6-(2-{4-[(ethylsulfonyl)oxy]phenyl}ethoxy)pyridin-3-yl]-2-methoxypropanoate

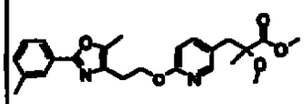
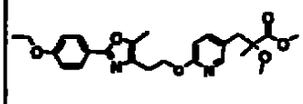
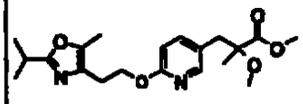
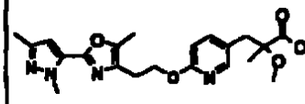
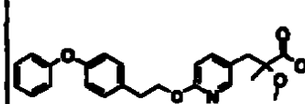
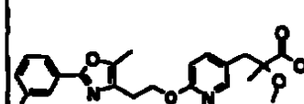


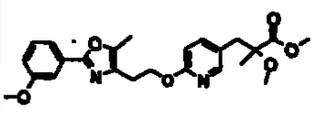
Preparations d-23 to d-38

Preparations d-23 to d-38 were prepared by procedures analogous to those used for Preparation d-22.

Preparation #	Structure	^{1}H NMR	MS (*m/z*) (LR or HR)
d-23			
d-24			

d-25		($CDCl_3$, 300 MHz): 7.90-7.99 (3H, m), 7.35-7.47 (4H, m), 6.65 (1H, d, J = 8.5 Hz), 4.27 (2H, t, J = 6.3 Hz), 4.17 (2H, t, J = 7.0 Hz), 3.29 (3H, s), 2.91 (2H, q, J = 14.1 Hz), 2.86 (2H, t, J = 7.4 Hz), 2.27 (3H, s), 2.15 (3H, s), 2.13 (2H, m), 1.25 (3H, t, J = 7.2 Hz)	for LR 439 $(M+H)^+$
d-26		($CDCl_3$, 400 MHz): 7.91-7.88 (3H, m), 7.41 (1H, dd, J = 8.8, 2.5 Hz), 7.39-7.36 (2H, m), 6.62 (1H, d, J = 8.3 Hz), 4.51 (2H, t, J = 6.8 Hz), 3.70 (3H, s), 3.28 (3H, s), 2.97-2.93 (3H, m), 2.86 (1H, d, J = 14.2 Hz), 2.32 (3H, s), 1.32 (3H, s)	for LR 445 $(M+H)^+$
d-27		($CDCl_3$, 400 MHz): 8.07 (2H, d, J = 8.07), 7.91 (1H, d, J = 2.3 Hz), 7.66 (2H, d, J = 8.3 Hz), 7.41 (1H, dd, J = 8.5, 2.4 Hz), 6.62 (1H, d, J = 8.3 Hz), 4.52 (2H, t, J = 6.7 Hz), 3.70 (3H, s), 3.28 (3H, s), 2.97 (2H, t, J = 6.7 Hz), 2.95 (1H, d, J = 14.2 Hz), 2.86 (1H, d, J = 14.2 Hz), 2.34 (3H, s), 1.33 (3H, s)	for LR 479 $(M+H)^+$
d-28		($CDCl_3$, 400 MHz): 7.90 (1H, d, J = 2.3 Hz), 7.41 (1H, dd, J = 8.5, 2.4 Hz), 6.61 (1H, d, J = 8.3 Hz), 4.42 (2H, t, J = 6.8 Hz), 3.71 (3H, s), 3.28 (3H, s), 2.95 (1H, d, J = 13.9 Hz), 2.86 (1H, d, J = 14.2 Hz), 2.86 (2H, t, J = 7.1 Hz), 2.67 (1H, tt, J = 11.6, 3.5 Hz), 2.19 (3H, s), 2.02-1.98 (2H, m), 1.81-1.77 (2H, m), 1.69-1.65 (1H, m), 1.54-1.46 (2H, m), 1.38-1.31 (2H, m), 1.33 (3H, s), 1.28-1.24 (1H, m)	for LR 417 $(M+H)^+$
d-29		($CDCl_3$, 400 MHz): 7.92 (1H, d, J = 2.3 Hz), 7.85 (2H, dd, J = 8.0, 1.6 Hz), 7.41 (1H, dd, J = 8.5, 2.4 Hz), 7.39-7.35 (3H, m), 6.63 (1H, d, J = 8.6 Hz), 4.59 (2H, t, J = 7.0 Hz), 3.70 (3H, s), 3.28 (3H, s), 3.18 (2H, t, J = 7.0 Hz), 2.95 (1H, d, J = 14.2 Hz), 2.87 (1H, d, J = 14.2 Hz), 2.42 (3H, s), 1.33 (3H, s)	for LR 427 $(M+H)^+$
d-30		($CDCl_3$, 400 MHz): 7.90 (1H, d, J = 2.3 Hz), 7.41 (1H, dd, J = 8.5, 2.4 Hz), 7.33 (1H, d, J = 7.6 Hz), 7.21 (1H, d, J = 7.6 Hz), 7.13 (1H, dt, J = 7.6, 1.0 Hz), 6.97 (1H, dt, J = 7.8, 1.3 Hz), 6.60 (1H, d, J = 8.6 Hz), 4.56 (2H, t, J = 5.4 Hz), 3.92 (2H, t, J = 5.4 Hz), 3.70 (3H, s), 3.28 (6H, s), 2.95 (1H, d, J = 13.9 Hz), 2.86 (1H, d, J = 14.2 Hz), 1.32 (3H, s)	for LR 400 $(M+H)^+$

d-31		($CDCl_3$, 400 MHz): 7.91 (1H, d, J = 2.3 Hz), 7.81 (1H, s), 7.75 (1H, d, J = 7.8 Hz), 7.41 (1H, dd, J = 8.5, 2.4 Hz), 7.29 (1H, t, J = 7.7 Hz), 7.19 (1H, d, J = 7.6 Hz), 6.62 (1H, d, J = 8.3 Hz), 4.52 (2H, t, J = 6.8 Hz), 3.70 (3H, s), 3.28 (3H, s), 2.96 (2H, t, J = 6.8 Hz), 2.95 (1H, d, J = 13.9 Hz), 2.86 (1H, d, J = 13.9 Hz), 2.38 (3H, s), 2.32 (3H, s), 1.33 (3H, s)	for LR 425 $(M+H)^+$
d-32		($CDCl_3$, 400 MHz): 7.91 (1H, d, J = 2.0 Hz), 7.89-7.86 (2H, m), 7.59 (1H, dd, J = 8.5, 2.2 Hz), 6.92-6.90 (2H, m), 6.62 (1H, d, J = 8.3 Hz), 4.51 (2H, t, J = 6.8 Hz), 4.06 (2H, q, J = 7.1 Hz), 3.70 (3H, s), 3.28 (3H, s), 2.95 (2H, t, J = 6.8 Hz), 2.96 (1H, d, J = 13.9 Hz), 2.87 (1H, d, J = 13.9 Hz), 2.30 (3H, s), 1.42 (3H, t, J = 7.1 Hz), 1.33 (3H, s)	for LR 455 $(M+H)^+$
d-33		($CDCl_3$, 400 MHz): 7.90 (1H, d, J = 2.3 Hz), 7.41 (1H, dd, J = 8.5, 2.4 Hz), 6.61 (1H, d, J = 8.3 Hz), 4.42 (2H, t, J = 6.8 Hz), 3.70 (3H, s), 3.28 (3H, s), 3.00-2.93 (1H, m), 2.95 (1H, d, J = 14.2 Hz), 2.86 (2H, t, J = 6.8 Hz), 2.86 (1H, d, J = 14.2 Hz), 2.20 (3H, s), 1.33 (3H, s), 1.30 (3H, s), 1.28 (3H, s)	for LR 377 $(M+H)^+$
d-34		($CDCl_3$, 400 MHz): 7.91 (1H, d, J = 2.3 Hz), 7.42 (1H, dd, J = 8.5, 2.4 Hz), 6.61 (1H, d, J = 8.3 Hz), 6.48 (1H, s), 4.51 (2H, t, J = 6.7 Hz), 4.15 (3H, s), 3.71 (3H, s), 3.28 (3H, s), 2.96 (1H, d, J = 13.9 Hz), 2.94 (2H, t, J = 6.8 Hz), 2.87 (1H, d, J = 13.9 Hz), 2.30 (3H, s), 2.27 (3H, s), 1.33 (3H, s)	for LR 429 $(M+H)^+$
d-35		($CDCl_3$, 400 MHz): 7.91 (1H, d, J = 2.3 Hz), 7.42 (1H, dd, J = 8.0, 1.9 Hz), 7.33-7.28 (2H, m), 7.23 (2H, d, J = 8.6 Hz), 7.08-7.04 (1H, m), 6.99-6.92 (4H, m), 6.64 (1H, d, J = 8.6 Hz), 4.45 (2H, t, J = 7.1 Hz), 3.70 (3H, s), 3.20 (3H, s), 3.04 (2H, t, J = 7.0 Hz), 2.92 (1H, d, J = 14.2 Hz), 2.87 (1H, d, J = 14.2 Hz), 1.33 (3H, s)	for LR 422 $(M+H)^+$
d-36		($CDCl_3$, 400 MHz): 7.90 (1H, d, J = 2.3 Hz), 7.42 (1H, dd, J = 8.5, 2.4 Hz), 7.28 (2H, d, J = 8.6 Hz), 7.13 (2H, d, J = 8.1 Hz), 6.63 (1H, d, J = 8.3 Hz), 4.46 (2H, t, J = 6.8 Hz), 3.71 (3H, s), 3.28 (3H, s), 3.06 (2H, t, J = 6.8 Hz), 2.95 (1H, d, J = 14.2 Hz), 2.86 (1H, d, J = 13.9 Hz), 1.33 (3H, s)	for LR 414 $(M+H)^+$
d-37		($CDCl_3$, 400 MHz): 7.91 (1H, d, J = 2.0 Hz), 7.74 (1H, d, J = 7.8 Hz), 7.41 (1H, dd, J = 8.2, 2.5 Hz), 7.34 (1H, t, J = 7.7 Hz), 7.38 (1H, s), 7.18 (1H, d, J = 8.1 Hz), 6.62 (1H, d, J = 8.3 Hz), 4.51 (2H, t, J = 6.7 Hz), 3.70 (3H, s), 3.28 (3H, s), 2.96 (2H, t, J = 6.8 Hz), 2.95 (1H, d, J =	for LR 429 $(M+H)^+$

		13.9 Hz), 2.86 (1H, d, *J* = 13.9 Hz), 2.32 (3H, s), 1.32 (3H, s)	
d-38		(CDCl$_3$, 400 MHz): 7.91 (1H, d, *J* = 2.0 Hz), 7.41 (1H, dd, *J* = 8.5, 2.4 Hz), 7.34-7.29 (2H, m), 6.96-6.93 (2H, m), 6.62 (1H, d, J = 8.5 Hz), 4.52 (2H, t, *J* = 6.8 Hz), 3.70 (3H, s), 3.28 (3H, s), 2.96 (2H, t, *J* = 6.8 Hz), 2.95 (1H, d, *J* = 13.9 Hz), 2.86 (1H, d, *J* = 13.9 Hz), 2.32 (3H, s), 2.16 (3H, s), 1.32 (3H, s)	for LR 441 $(M+H)^+$

The compounds of the invention have been tested for activities against PPAR-gamma and PPAR-alpha. The activities are tabulated below in Ki (μm).

Example #	PPAR-gamma Ki (μm)	PPAR-alpha Ki (μm)	Example #	PPAR-gamma Ki (μm)	PPAR-alpha Ki (μm)	Example #	PPAR-gamma Ki (μm)	PPAR-alpha Ki (μm)
A-02		0.55	B-02		2.2	C-03		2.9
A-03	10	19	B-03	31	9	C-05		15
A-05 E/M	0.33	2.8	B-04	1.5	48	C-06	9.5	41
A-05 S/E	3.4	7.5	B-05	1.33	2.04	C-07	11	22
A-05 S/E	0.19	1.1	B-05	2.9	3.2	C-09	1.4	4.6
A-07		0.12	B-05	2	3.6	C-10	2.1	19
A-10	1.5	4.4	B-06	0.37	0.13	C-11	2	25
A-11	0.58	0.12	B-07	0.65	12	C-12	1.6	9.4
A-12	0.051	0.35	B-08	0.48	3.1	C-14	8	3.2
A-13	3.5	10	B-09	1.9	2.2	C-15	14	3.2
A-14	1.3	0.15	B-10	0.17	0.19	C-17	26	3.2
A-15	1.2	0.16	B-11	7.9	0.96	C-18	3.5	0.065
A-16	2.8	1.5	B-12	33	0.3	C-20	1.5	3.1
A-17	1.9	1.6	B-13		9	C-21	0.053	0.066
A-18	1.7	14	B-14	2.3	0.021	C-22	0.8	2.1
A-19	0.059	0.7	B-16	1.8	0.084	C-23	0.19	2.5
A-20	0.18	0.14	B-17	1.2	0.047	C-24	0.083	0.022
A-21	0.068	0.31	B-18		0.082	C-25	0.066	0.018
A-22	0.17	0.85	B-19	0.74	0.34	C-26	0.068	0.016
A-23	0.39	0.18	B-20		1.6	C-27	0.026	0.015
A-24	0.78	0.018	B-21	0.99	4	C-28	0.03	0.088
A-25	3.2	4.2	B-22	0.15	0.46	C-29	0.006	0.12
A-26	0.15	0.33	B-23	3.4	2.7	C-30	0.033	0.11
A-27	2.4	1.3	B-24	1.6	1	C-31	0.026	0.093
A-28 E/M	0.044	0.93	B-27		0.22	C-32	0.035	0.15
A-28 S/E	0.081	1.1	B-28		7.8	C-33	0.05	0.01
A-28 S/E	0.94	2.9	C-02		0.39	C-36	1.7	21

E/M is defined as enantiomeric mixture, including racemic mixture.
S/E is defined as single enantiomer.

Example #	PPAR-gamma Ki (μm)	PPAR-alpha Ki (μm)	Example #	PPAR-gamma Ki (μm)	PPAR-alpha Ki (μm)	Example #	PPAR-gamma Ki (μm)	PPAR-alpha Ki (μm)
C-38	7.2		C-64	0.052	0.014	C-90	0.017	0.11
C-40	3.7	0.7	C-66	0.023	0.031	C-91	0.39	1.8
C-42	33	13	C-67	0.044	0.25	C-92	1.1	2.8
C-44		36	C-68	4.2		C-93	0.011	0.3
C-45	0.22	7.7	C-69	1.1	2.5	C-94	7	
C-46	2	3.5	C-70		6.4	C-95	0.97	8.6
C-47	3.5	8.3	C-71		9.7	D-02	0.46	0.29
C-48	0.018	0.24	C-72		7.1	D-03	0.011	0.3
C-48 E/M	0.15	0.31	C-73	0.042		D-04	0.44	0.29
C-48 S/E	0.014	0.047	C-74	0.84	0.9	D-05	2.8	
C-48 S/E		2.4	C-74 S/E			D-06	0.027	0.13
C-49	0.21	1.6	C-74 S/E	0.47	4.2	D-07	0.017	0.32
C-49	21	41	C-75	0.82		D-08	0.002	0.015
C-49	0.043	0.34	C-76	2.3	7.3	D-09	0.061	0.05
C-50	0.043	1.1	C-77	0.15	2.9	D-10	0.019	0.033
C-51	0.18	2.9	C-78	0.006	0.015	D-11	6.2	5.1
C-52	0.3	0.15	C-78 S/E	3.9		D-12	8.1	
C-53	0.093	0.84	C-78 S/E	0.003	0.014	D-13	0.36	0.19
C-53 S/E	3.6		C-79	0.007	0.015	D-14	1.5	2.6
C-53 S/E	0.027	0.4	C-80	0.062	0.053	D-15	0.35	0.22
C-54	0.02	1.2	C-81	0.015	0.75	D-16	6.4	
C-55	6		C-82	0.016		D-17	0.031	0.91
C-56	0.061	0.078	C-83	0.008	0.004	D-18	0.45	0.62
C-57	1.1	1.8	C-84	0.021	0.084	D-19	1.7	6.4
C-59	0.009	0.054	C-85	0.004	0.013	D-20	0.48	0.84
C-60	0.015	0.065	C-86	0.005	0.013	D-21	2.1	10
C-61	0.31	0.24	C-87	0.012	0.025	D-23 E/M	0.073	6.5
C-63	0.094	0.021	C-89	0.04	0.03	D-23 S/E	5	

E/M is defined as enantiomeric mixture, including racemic mixture.
S/E is defined as single enantiomer

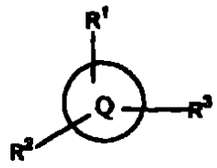
Example #	PPAR-gamma Ki (μm)	PPAR-alpha Ki (μm)	Example #	PPAR-gamma Ki (μm)	PPAR-alpha Ki (μm)
D-23 S/E	0.039	1.1	D-33	0.69	0.55
D-24	no SPA	no SPA	D-34	9.1	3.2
D-24	0.58	0.93	D-35	0.56	0.33
D-25	2.9		D-35 S/E	0.27	0.57
D-26	no SPA	no SPA	D-35 S/E	4.8	9
D-26 S/E	1.9		D-36	0.23	0.73
D-26 S/E	0.042	0.67	D-37	0.53	4.7
D-27	7.8		D-38	9.6	
D-28	1.6	4.8	D-39	5	
D-29	0.4	0.8	D-40	9.6	1.8
D-29 S/E	1.2		D-41		5.9
D-29 S/E	0.69	3	D-42	0.7	1
D-31	1	0.088	D-44	0.15	2.6
D-32	1.5	0.059	D-45	0.058	0.09

E/M is defined as enantiomeric mixture, including racemic mixture.
S/E is defined as single enantiomer

While the invention has been illustrated by reference to specific and preferred embodiments, those skilled in the art will recognize that variations and modifications may be made through routine experimentation and practice of the invention. Thus, the invention is intended not to be limited by the foregoing description, but to be defined by the appended claims and their equivalents.

We Claim:

1. A compound of formula (I):



(I)

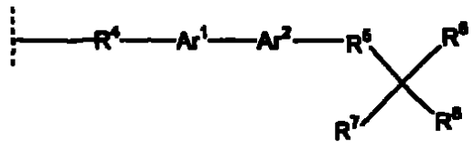
or a pharmaceutically acceptable salt or solvate thereof, wherein:

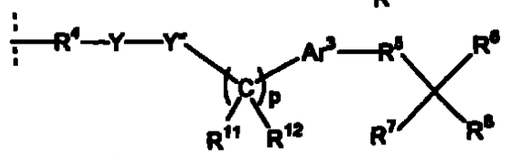
Ring Q is $(C_6$-$C_{10})$aryl or (4-10)-membered heterocyclyl;

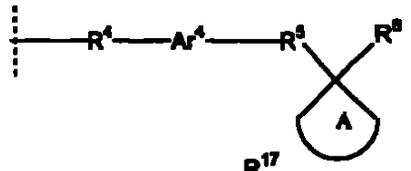
R^1 is H, halo, $(C_1$-$C_8)$alkyl, $(C_1$-$C_8)$alkoxy, CN, CF_3, -O-CF_3, -O-SO_2-$(C_1$-$C_8)$alkyl, -O-SO_2-$(CR^{11}R^{12})_t(C_6$-$C_{10})$aryl, -$(CR^{11}R^{12})_t(C_3$-$C_{10})$cycloalkyl-$(CR^{11}R^{12})_t$, -$(CR^{11}R^{12})_t(C_3$-$C_{10})$cycloalkyl-$(CR^{11}R^{12})_t$-O-, -$(CR^{11}R^{12})_t(C_6$-$C_{10})$aryl-$(CR^{11}R^{12})_t$, -$(CR^{11}R^{12})_t(C_6$-$C_{10})$aryl-$(CR^{11}R^{12})_t$-O-, -$(CR^{11}R^{12})_t$-(4-10)-membered heterocyclyl-$(CR^{11}R^{12})_t$, or -$(CR^{11}R^{12})_t$-(4-10)-membered heterocyclyl-$(CR^{11}R^{12})_t$-O-; wherein the ring carbon atoms of R^1 are optionally substituted by 1 to 3 R^{13} groups; and the ring nitrogen atoms of R^1 are optionally substituted by 1 to 3 $(C_1$-$C_8)$alkyl;

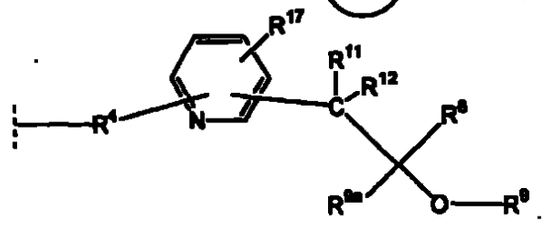
R^2 is H, $(C_1$-$C_8)$alkyl, -$(CR^{11}R^{12})_t$-$(C_3$-$C_{10})$cycloalkyl, -$(CR^{11}R^{12})_t$-$(C_6$-$C_{10})$aryl, or -$(CR^{11}R^{12})_t$(4-10)-membered heterocyclyl; and wherein the carbon atoms of R^2 are optionally substituted by 1 to 3 R^{13} groups; and the ring nitrogen atoms of R^2 are optionally substituted by 1 to 3 $(C_1$-$C_8)$alkyl;

R^3 is selected from the group consisting of:

A)  ;

B)  ;

C)  ; and

D)  ;

Y is -(C=O)- or -SO_2-;

Y" is NR^{10} or –O-;

p is 0, 1, or 2;

each q, r, and t are independently 0, 1, 2, 3, 4, or 5;

each n is independently 0, 1, 2, 3, or 4;

each k is independently 1, 2, or 3;

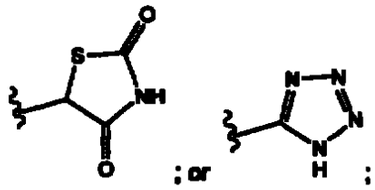
each m and s are independently 0, 1, 2, or 3;

each j is 0, 1, or 2;

Each R^4 is $-(CR^{11}R^{12})_n-$, $-(CR^{11}R^{12})_m-S-(CR^{11}R^{12})_n-$, $-(CR^{11}R^{12})_n-NR^{10}-$, $-(CR^{11}R^{12})_n-NR^{10}-(CR^{11}R^{12})_n-O-$, $-(CR^{11}R^{12})_n-O-(CR^{11}R^{12})_k-NR^{10}-$, $-(CR^{11}R^{12})_n-O-(CR^{11}R^{12})_n-$, $-(CR^{11}R^{12})_n-O-(CR^{11}R^{12})_k-O-(CR^{11}R^{12})_n-$, $-(CR^{11}R^{12})_n-CR^{11}=CR^{12}-(CR^{11}R^{12})_n-$, or $-CH=CH-(CR^{11}R^{12})-O-(CH_2)_n-$;

Each R^5 is a bond or $-(CR^{11}R^{12})_m-Z-(CR^{11}R^{12})_n$; wherein Z is $-CR^{11}R^{12}-$, $-O-$, $-NR^{10a}-$, or $-S(O)_j-$;

Each R^6 is $-(C=O)-OH$, $-(C=O)-OM^+$, $-(C=O)-(C_1-C_8)$alkyl, $-(C=O)-O-(C_1-C_8)$alkyl, $-(C=O)-NR^{10}R^{11}$, $-(C=O)-NR^{10}-SO_2-R^{11}$, $-SO_2-NH-R^{10}$, $-NH-SO_2-R^{10}$, $-(C=O)-NH-C\equiv N$, or R^6 has a formula:



; or

;

M^+ is an alkali metal cation or an alkaline earth metal cation;

Each R^7 and R^8 is independently H, (C_1-C_8)alkyl, (C_1-C_8)alkoxy, $-(CR^{11}R^{12})_k(C_3-C_{10})$cycloalkyl, $-(CR^{11}R^{12})_k(C_6-C_{10})$aryl, $-(CR^{11}R^{12})_k(C_6-C_{10})$aryl-O-, $-(CR^{11}R^{12})_k$(4-10)-membered heterocyclyl or $-(CR^{11}R^{12})_k$(4-10)-membered heterocyclyl-O-;

Or R^7 and R^8 may optionally be taken together with the carbon to which they are attached to form a (C_3-C_{10})cycloalkyl or a (3-10)-membered heterocyclyl;

Each of Ar^1, Ar^2, Ar^3, and Ar^4 represents (C_6-C_{10})aryl or (5-10)-membered heterocyclyl; wherein the ring carbon atoms of each of Ar^1, Ar^2, Ar^3, and Ar^4 are optionally substituted by 1 to 3 R^{13} groups;

Ring A represents a 3, 4, 5, 6 or 7-membered ring optionally containing 1 to 4 heteroatoms which may be the same or different and which are selected from $-N(R^{10a})-$, O, and $S(O)_j$, wherein j is 0, 1, or 2, with the proviso that the ring does not contain two adjacent O or $S(O)_j$ atoms, and wherein the carbon atoms of the ring A moiety are optionally substituted by 1 to 3 R^{13} groups;

R^9 is (C_1-C_8)alkyl, $-(CR^{11}R^{12})_t(C_6-C_{10})$aryl or $-(CR^{11}R^{12})_t$(4-10)-membered heterocyclyl, wherein t is independently 0, 1, 2, 3, 4, or 5, wherein said R^9 groups are substituted with 1 to 3 groups independently selected from $-(CR^{11}R^{12})_nNR^{10}R^{11}$,

$-(CR^{11}R^{12})_qNR^{10}(C_1-C_8)$alkanoyl, $-(CR^{11}R^{12})_qO(CR^{11}R^{12})_rR^{10}$, and $-(CR^{11}R^{12})_qR^{10}$; and wherein the heterocyclyl, aryl and alkyl moieties of the foregoing groups are optionally substituted with 1 to 3 R^{13} groups;

R^{9a} and R^{10} are independently H or (C_1-C_8)alkyl;

R^{11} and R^{12} are independently H, (C_1-C_8)alkyl, hydroxy, or (C_1-C_8)alkoxy;

R^{10a} is selected from H, (C_1-C_8)alkyl, $-(C=O)-R^{14}$, $-SO_2NR^{15}R^{16}$, or $-S(O)_t(C_1-C_8)$alkyl;

Each R^{13} and R^{13a} are independently selected from the group consisting of halo, cyano, nitro, trifluoromethoxy, trifluoromethyl, azido, hydroxy, (C_1-C_8)alkoxy, (C_1-C_{10})alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, $-O-(CR^{11}R^{12})_s-O-(CR^{11}R^{12})_{s'}-$, $-(C=O)-R^{14}$, $-(C=O)-O-R^{15}$, $-O-(C=O)-R^{15}$, $-NR^{15}(C=O)-R^{16}$, $-NR^{15}(C=O)-O-R^{16}$, $-(C=O)-NR^{15}R^{16}$, $-NR^{15}R^{16}$, $-NR^{15}OR^{16}$, $-SO_2NR^{15}R^{16}$, $-S(O)_t(C_1-C_8)$alkyl, $-O-SO_2-R^{14}$, $-NR^{15}-SO_2-R^{16}$, $R^{16}-(CR^{11}R^{12})_t(C_6-C_{10}$ aryl), $-(CR^{11}R^{12})_t$(4-10)-membered heterocyclyl, $-(CR^{11}R^{12})_q(C=O)(CR^{11}R^{12})_t(C_6-C_{10})$aryl, $-(CR^{11}R^{12})_q(C=O)(CR^{11}R^{12})_t$(4-10)-membered heterocyclyl, $-(CR^{11}R^{12})_qO(CR^{11}R^{12})_q(C_6-C_{10})$aryl, $-(CR^{11}R^{12})_qO(CR^{11}R^{12})_q$(4-10)-membered heterocyclyl, $-(CR^{11}R^{12})_qSO_2(CR^{11}R^{12})_t(C_6-C_{10})$aryl, and $-(CR^{11}R^{12})_qSO_2(CR^{11}R^{12})_t$(4-10)-membered heterocyclyl; 1 or 2 ring carbon atoms of the heterocyclic moieties of the foregoing R^{13} and R^{13a} groups are optionally substituted with an oxo (=O) moiety, and the alkyl, alkenyl, alkynyl, aryl and heterocyclic moieties of the foregoing R^{13} and R^{13a} groups are optionally substituted with 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-OR^{15}$, $-(C=O)-R^{15}$, $-(C=O)-O-R^{15}$, $-O-(C=O)-R^{15}$, $-NR^{15}(C=O)-R^{15}$, $-(C=O)-NR^{15}R^{16}$, $-NR^{15}R^{16}$, $-NR^{15}OR^{16}$, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, $-(CR^{11}R^{12})_t(C_6-C_{10})$aryl, and $-(CR^{11}R^{12})_t$(4-10)-membered heterocyclyl;

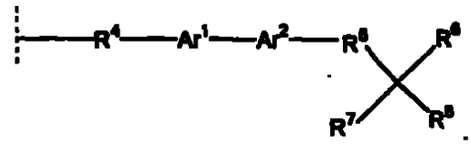
each R^{14}, R^{15}, and R^{16} is independently selected from H, (C_1-C_8)alkyl, $-(CR^{11}R^{12})_t(C_6-C_{10})$aryl, and $-(CR^{11}R^{12})_t$(4-10)-membered heterocyclyl; 1 or 2 ring carbon atoms of the heterocyclic group are optionally substituted with an oxo (=O) moiety, and the alkyl, aryl and heterocyclic moieties of the foregoing R^{14}, R^{15} and R^{16} groups are optionally substituted with 1 to 3 substituents independently selected from halo, cyano, nitro, $-NR^{11}R^{12}$, trifluoromethyl, trifluoromethoxy, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, hydroxy, and (C_1-C_8) alkoxy;

R^{17} is H, (C_1-C_8)alkyl, $-O-(C_1-C_8)$alkyl, halo, CN, OH, CF_3, or $-O-CF_3$;

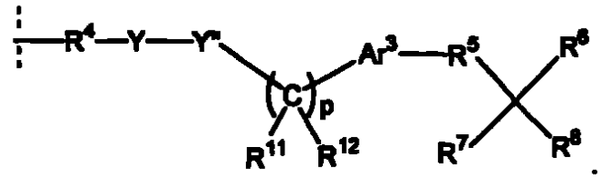
and wherein any of the above-mentioned substituents comprising a CH_3 (methyl), CH_2 (methylene), or CH (methine) group which is not attached to a halo, SO or SO_2 group or to a N, O or S atom optionally bears on said group a

substituent selected from hydroxy, halo, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, $-NH_2$, $-NH(C_1-C_8)$alkyl, and $-N((C_1-C_8)alkyl)_2$.

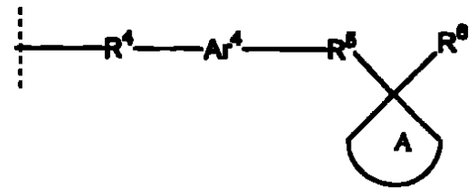
2. The compound according to claim 1 wherein R^3 is

A) 

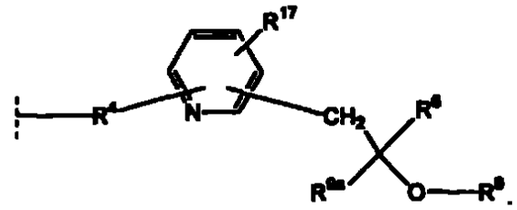
3. The compound according to claim 1 wherein R^3 is

B) 

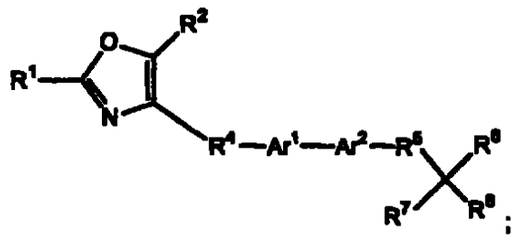
4. The compound according to claim 1 wherein R^3 is

C) 

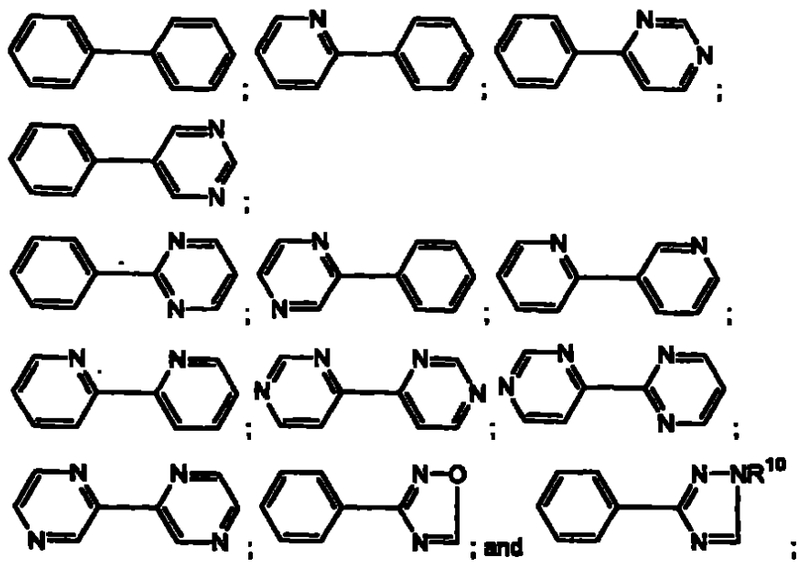
5. The compound according to claim 1 wherein R^3 is

D) 

6. The compound according to claim 2 having a formula:



wherein said $-Ar^1-Ar^2-$ is selected from the group consisting of:



wherein the ring carbon atoms of each of Ar^1 and Ar^2 are optionally substituted by 1 to 3 R^{13} groups selected from the group consisting of halo, (C_1-C_8)alkyl, and (C_1-C_8)alkoxy.

7. The compound according to claim 2 selected from the group consisting of

1-({3'-[2-(5-Methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-1,1'-biphenyl-3-yl}oxy)cyclobutanecarboxylic acid (Example A-4);

2-({3'-[2-(5-Methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-1,1'-biphenyl-3-yl}oxy)butanoic acid (Example A-5);

2-(3-{6-[2-(5-Methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridin-2-yl}phenoxy)butanoic acid (Example A-6);

1-(3-{6-[2-(5-Methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridin-2-yl}phenoxy)cyclobutanecarboxylic acid (Example A-7);

1-[(3'-{[2-(3-fluorophenyl)-5-methyl-1, 3-oxazol-4-yl]methoxy}biphenyl-3-yl)oxy]cyclobutanecarboxylic acid (Example A-11);

1-({3'-[3-(5-methyl-2-phenyl-1, 3-oxazol-4-yl)propoxy]biphenyl-3-yl}oxy)cyclobutanecarboxylic acid (Example A-12);

1-[(3'-{[5-(4-methoxyphenyl)-1,2,4-oxadiazol-3-yl]methoxy}biphenyl-3-yl)oxy]cyclobutanecarboxylic acid (Example A-17);

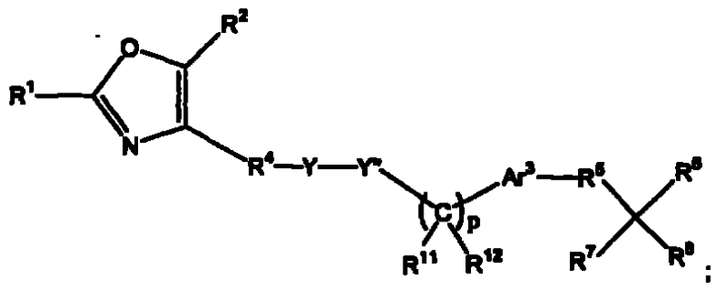
2-[(3'-{2-[2-(3-Fluorophenyl)-5-methyl-1,3-oxazol-4-yl]ethoxy}biphenyl-3-yl)oxy]-2-methylpropanoic acid (Example A-21);

2-methyl-2-({3'-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]biphenyl-3-yl}oxy)propanoic acid (Example A-24);

2-ethoxy-3-[3'-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]biphenyl-3-yl]propanoic acid (Example A-28);

and the pharmaceutically acceptable salts thereof.

8. The compound according to claim 3 having a formula:



wherein Y is -(C=O)- or -SO_2-, Y'' is NR^{10}, and p is 1.

9. The compound according to claim 3 selected from the group consisting of

2-Methyl-2-[3-[([[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]carbonyl}amino)methyl]phenoxy}propanoic acid (Example B-5);

2-methyl-2-[3-[([[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]carbonyl}amino)methyl]phenoxy}propanoic acid (Example B-6);

2-methyl-2-[4-[([[3-(5-methyl-2-phenyl-1,3-oxazol-4-yl)propoxy]carbonyl}amino)methyl]phenoxy}propanoic acid (Example B-7);

2-[3-fluoro-4-[([[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]carbonyl}amino)methyl]phenoxy}-2-methylpropanoic acid (Example B-9);

2-[3-[([[2-(5-Methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]carbonyl}amino)methyl]phenoxy}butanoic acid (Example B-13);

2-[3-[([[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]carbonyl}amino)methyl]phenoxy}butanoic acid (Example B-14);

1-[3-[([[2-(5-Methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]carbonyl}amino)methyl]phenoxy}cyclobutanecarboxylic acid (Example B-15);

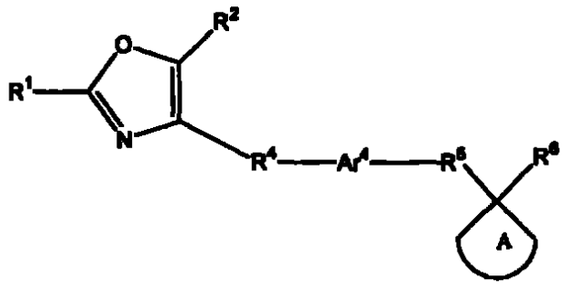
2-methyl-2-(3-[[([[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethyl]amino}carbonyl)oxy]methyl}phenoxy)propanoic acid (Example B-21);

2-ethoxy-3-[3-[([[3-(5-methyl-2-phenyl-1,3-oxazol-4-yl)propoxy]carbonyl}amino)methyl]phenyl}propanoic acid (Example B-23);

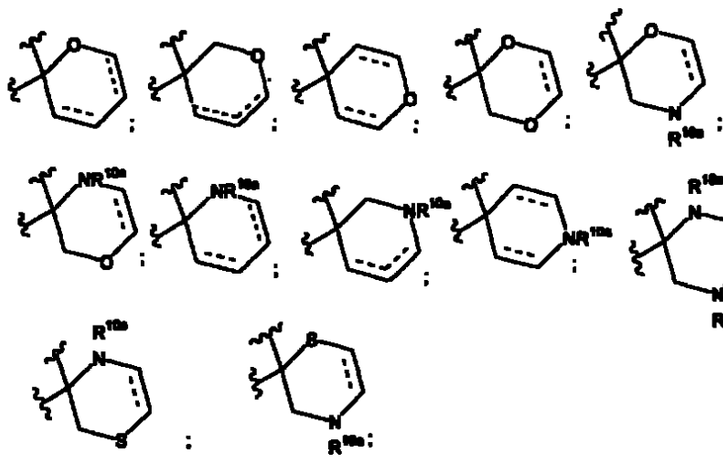
2-ethoxy-3-[3-[([[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]carbonyl}amino)methyl]phenyl}propanoic acid (Example B-24);

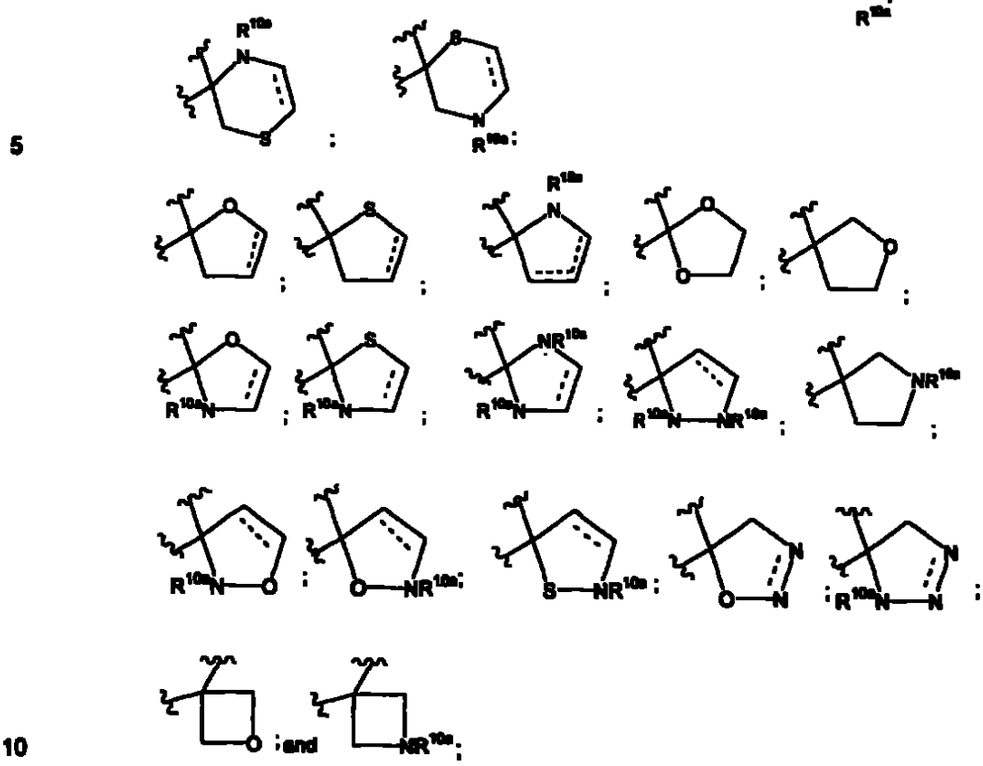
and the pharmaceutically acceptable salts thereof.

10. The compound according to claim 4 having a formula:



wherein said ring A is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,





wherein — is an optional double bond.

11. The compound according to claim 4 selected from the group consisting of

1-{4-[3-(5-methyl-2-phenyl-1,3-oxazol-4-yl)propoxy]benzyl}cyclobutanecarboxylic acid (Example C-16);

1-{4-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]benzyl}cyclobutanecarboxylic acid (Example C-19);

2-({6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridin-3-yl}methyl)tetrahydrofuran-2-carboxylic acid (Example C-48);

2-({5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridin-2-yl}methyl)tetrahydrofuran-2-carboxylic acid (Example C-49);

2-({6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridin-3-yl}methyl)tetrahydro-2*H*-pyran-2-carboxylic acid (Example C-58);

2-[({6-[2-[2-(3-chlorophenyl)-5-methyl-1,3-oxazol-4-yl]ethoxy}pyridin-3-yl)methyl]tetrahydrofuran-2-carboxylic acid (Example C-59);

2-[({6-[2-[2-(3-methoxyphenyl)-5-methyl-1,3-oxazol-4-yl]ethoxy}pyridin-3-yl)methyl]tetrahydrofuran-2-carboxylic acid (Example C-62);

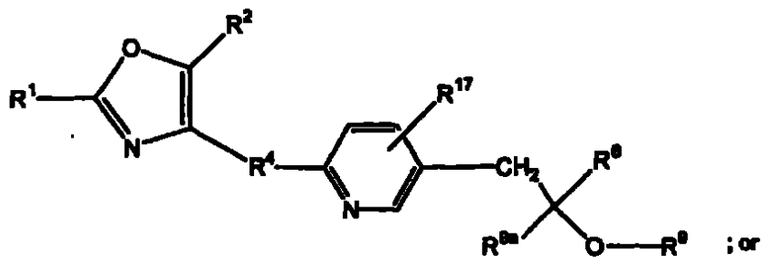
2-{5-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyrazin-2-ylmethyl}-tetrahydro-furan-2-carboxylic acid (Example C-77);

-{4-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]benzyl}tetrahydrofuran-2-carboxylic acid (Example C-78);

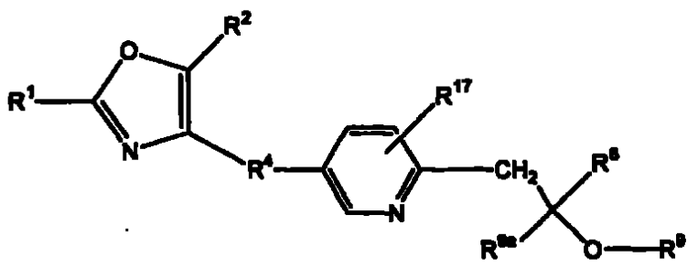
2-{6-[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethoxy]-naphthalen-2-ylmethyl}-tetrahydro-furan-2-carboxylic acid (Example C-91);

and the pharmaceutically acceptable salts thereof.

12. The compound according to claim 5 having a formula:



; or



13. The compound according to claim 12 selected from the group consisting of

2-ethoxy-3-{6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]pyridin-3-yl}propanoic acid (Example D-1);

2-methoxy-3-(6-{2-[5-methyl-2-(3-methylphenyl)-1,3-oxazol-4-yl]ethoxy}pyridin-3-yl)propanoic acid (Example D-3);

2-methoxy-3-{6-[2-(4-phenoxyphenyl)ethoxy]pyridin-3-yl}propanoic acid (Example D-13);

2-ethoxy-3-[6-(2-{4-[(phenylsulfonyl)oxy]phenyl}ethoxy)pyridin-3-yl]propanoic acid (Example D-17);

2-Ethoxy-3-{5-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridin-2-yl}-propionic acid (Example D-23);

2-Methoxy-2-methyl-3-{6-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propoxy]-pyridin-3-yl}-propionic acid (Example D-27);

2-Methoxy-2-methyl-3-{5-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-pyridin-2-yl}-propionic acid (Example D-29);

3-(6-{2-[2-(4-Chloro-phenyl)-5-methyl-oxazol-4-yl]-ethoxy}-pyridin-3-yl)-2-methoxy-2-methyl-propionic acid (Example D-30);

2-Methoxy-2-methyl-3-{6-[2-(5-methyl-2-phenyl oxazol-4-yl)-ethoxy]-pyridin-3-yl}-propionic acid (Example D-35);

2-Methoxy-3-(6-{2-[2-(3-methoxy-phenyl)-5-methyl-oxazol-4-yl]-ethoxy}-pyridin-3-yl)-2-methyl-propionic acid (Example D-43);

and the pharmaceutically acceptable salts thereof.

14. A method of treating non-insulin dependent diabetes mellitus, polycystic ovarian syndrome, obesity, hyperglycemia, hyperlipidemia, hypercholesteremia, atherosclerosis, hypertriglyceridemia, hyperinsulinemia, abnormal insulin and/or evidence of glucose disorders, insulin resistance syndrome, and PPAR-related disorders in a mammal comprising administering to the mammal in need thereof a therapeutically effective amount of an alpha substituted carboxylic acid compound according to claim 1.

15. A composition comprising at least one compound according to claim 1 and a pharmaceutically acceptable carrier thereof; said compound is optionally in combination with other agents such as α-glucosidase inhibitors, aldose reductase inhibitors, biguanide preparations, statin base compounds, squalene synthesis inhibitors, fibrate base compounds, LDL catabolism promoters and angiotensin-converting enzyme inhibitors.

ÁCIDOS CARBOXÍLICOS ALFA SUSTITUIDOS COMO MODULADORES PPAR

Antecedentes de la invención

Esta invención se refiere a ácidos carboxílicos alfa sustituidos que modulan las actividades del receptor activado - proliferador de peroxisomas (abreviadamente en inglés PPAR), preferiblemente dos o más de PPAR-α, PPAR-δ, o PPAR-γ, permitiéndoles que sean útiles en la modulación de glucosa en sangre y y el incremento de la sensibilidad a insulina en mamíferos. Esta invención también se refiere al tratamiento de trastornos relativos a PPAR, tales como diabetes, dislipidemia, obesidad y trastornos inflamatorios.

Los proliferadores de peroxisomas son un grupo estructuralmente diverso de compuestos que, cuando se administran a roedores, provocan incrementos espectaculares en el tamaño y número de peroxisomas hepáticos y renales, así como incrementos concomitantes en la capacidad de los peroxisomas para metabolizar ácidos grasos mediante un aumento de la expresión de las enzimas requeridas para el ciclo de β-oxidación. Los compuestos químicos incluidos en este grupo son la clase de fibratos de los fármacos hipolipidérmicos, herbicidas, y plastificantes de ftalatos (Reddy y Lalwani, *Crit. Rev. Toxicol.*, 12: 1 – 58 (1983)). La proliferación de los peroxisomas también se puede provocar mediante factores dietéticos o fisiológicos tales como una dieta alta en grasa y aclimatación al frío.

La comprensión del mecanismo por el que los proliferadores de los peroxisomas ejercen sus efectos pleiotrópicos se proporcionó mediante la identificación de un miembro de la superfamilia de los receptores de la

hormona nuclear activados por estos compuestos químicos (Isseman y Green, *Nature*, 347 - 645 – 650 (1990)). Este receptor, denominado PPAR-α, se mostró posteriormente que se activa mediante una diversidad de medios y de ácidos grasos de cadena larga y que estimula la expresión de genes que codifican la acil-CoA oxidasa y la hidratasa-deshidrogenasa (enzimas requeridas para la β-oxidación de los peroxisomas) en ratas, así como el citocromo P450 A46 en conejos, una Ω-hidrolasa de ácidos grasos.

El PPAR-α, activa la transcripción mediante la unión a elementos de la secuencia de DNA, denominados elementos de respuesta de proliferadores de peroxisomas (abreviadamente en inglés PPRE), como un heterodímero con el receptor retinoide X. El receptor retinoide X se activa mediante el ácido 9-cis retinoico (véase Kliewer, y col., *Nature*, 358: 771 – 774 (1992), Gearing, y col., *Proc. Natl. Acad. Sci. Estados Unidos*, 90: 1440 – 1444 (1993), Keller, y col., *Proc. Natl. Acad. Sci. Estados Unidos*, 90: 2160 – 2164 (1993), Heyman, y col., *Cell*, 68: 397 – 406 (1992), y Levin, y col., *Nature*, 355: 359 – 361 (1992)). Ya que el complejo PPAR-α –RXR se puede activar mediante los proliferadores de los peroxisomas y/o el ácido 9-cis retinoico, las vías de señalización del retinoide y de los ácidos grasos se ven que convergen en la modulación del metabolismo lipídico.

Desde el descubrimiento de PPAR-α, se han identificado isoformas adicionales de PPAR, por ejemplo PPAR-δ, o PPAR-γ, que se expresan de manera diferencial espacialmente. Cada receptor de PPAR muestra un patrón diferente de expresión de tejidos, y diferencias en activación mediante compuestos estructuralmente diversos. Por ejemplo, PPAR-γ se expresa más abundantemente en el tejido adiposo y a niveles inferiores en el músculo

esquelético, corazón, hígado, intestino, riñón, células endoteliales vasculares y de los músculos lisos así como macrófagos. Existen dos isoformas de PPAR-γ, identificadas como γ_1 y γ_2, respectivamente. El PPAR-γ media la señalización de los adipocitos, almacenamiento lipídico y el metabolismo de las grasas. La evidencia acumulada hasta la fecha soporta la conclusión de que el PPAR-γ es el principal, y quizás la única, diana molecular que media la acción sensibilizadora de la insulina de una clase de agentes antidiabéticos, las tiazolidina 2,4-dionas.

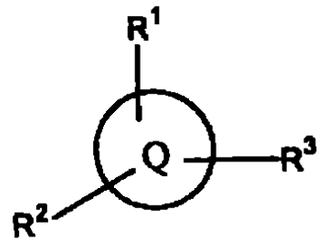
En un contexto de monoterapia o de terapia de combinación, los nuevos agentes antidiabéticos orales establecidos todavía se consideran que tienen una eficacia no uniforme e incluso limitada. La eficacia de las terapias antidiabéticas orales puede estar limitada, en parte, debido al escaso o limitado control glucémico, o escasa conformidad del paciente debido a los efectos secundarios inaceptables. Estos efectos secundarios incluyen edema, ganancia de peso, o incluso complicaciones más graves. Por ejemplo, se observa hipoglucemia en algunos pacientes que toman sulfonilureas. La metformina, una biguanida sustituida, puede producir diarrea y malestar gastrointestinal. Finalmente, edema, ganancia de peso, y en algunos casos, hepatotoxicidad, se han asociado a la administración de algunos agentes antidiabéticos de tiazolidina 2,4-diona. Es frecuente la terapia de combinación que usa dos o más de los agentes anteriores, pero generalmente solo conduce a mejoras incrementales en el control glucémico.

Como resultado, existe necesidad de agentes antidiabéticos que muestran activación combinada de PPAR-α y PPAR-γ que debería conducir al descubrimiento de fármacos eficaces reduciendo la glucosa y los triglicéridos

que tienen un gran potencial en el tratamiento de la diabetes tipo 2 y el síndrome metabólico (es decir, tolerancia a la glucosa alterada, resistencia a la insulina, hipertrigliceridemia y/u obesidad).

Sumario de la invención

La presente invención proporciona compuestos novedosos de fórmula (I):



o una sal o solvato farmacéuticamente aceptable del mismo, en la que :

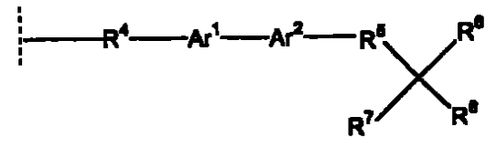
El anillo Q es arilo ($C_6 - C_{10}$) o heterociclilo de (4 – 10) eslabones;

R^1 es H, halo, alquilo ($C_1 - C_8$), alcoxi ($C_1 - C_8$), CN, CF_3, -O-CF_3, -O-SO_2-alquilo ($C_1 - C_8$), –O-SO_2–$(CR^{11}R^{12})_t$ arilo ($C_6 - C_{10}$), – $(CR^{11}R^{12})_t$ cicloalquil ($C_3 - C_{10}$) – $(CR^{11}R^{12})_t$, –$(CR^{11}R^{12})_t$ cicloalquil ($C_3 - C_{10}$) – $(CR^{11}R^{12})_t$– O –, – $(CR^{11}R^{12})_t$ aril ($C_6 - C_{10}$) – $(CR^{11}R^{12})_t$, -$(CR^{11}R^{12})_t$ aril ($C_6 - C_{10}$)$_t$ – $(CR^{11}R^{12})_t$–O–, –$(CR^{11}R^{12})_t$ heterociclil de (4 – 10) eslabones – $(CR^{11}R^{12})_t$, o –$(CR^{11}R^{12})_t$ heterociclil de (4 – 10) eslabones – $(CR^{11}R^{12})_t$–O–; en los que los átomos de carbono del anillo de R^1 están opcionalmente sustituidos por 1 a 3 grupos R^{13}; y los átomos de nitrógeno en el anillo de R^1 están opcionalmente sustituidos con 1 a 3 alquilo ($C_1 - C_8$);

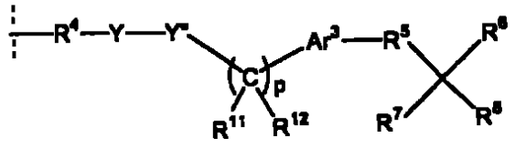
R^2 es H, alquilo ($C_1 - C_8$), –$(CR^{11}R^{12})_t$ – cicloalquilo ($C_3 - C_{10}$), –

$(CR^{11}R^{12})_t$ – arilo (C_6 – C_{10}), o – $(CR^{11}R^{12})_t$ heterociclilo de (4 – 10) eslabones; y en los que los átomos de carbono de R^2 están opcionalmente sustituidos con 1 a 3 grupos R^{13}; y los átomos de nitrógeno en el anillo de R^2 están opcionalmente sustituidos con 1 a 3 alquilo (C_1 – C_8);

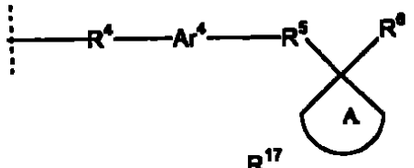
R^2 se selecciona entre el grupo constituido por:

A) 

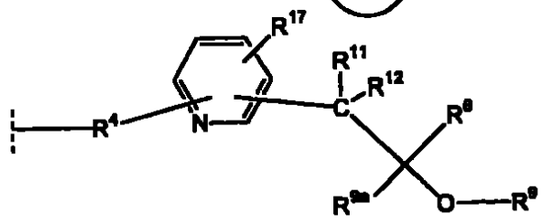
;

B) 

;

C) 

; y

D) 

;

Y es –(C=O) – o –SO_2–;

Y" es NR^{10} u –O–;

p es 0, 1, ó 2;

cada q, r, y t son independientemente 0, 1, 2, 3, 4, ó 5;

cada n es independientemente 0, 1, 2, 3 ó 4;

cada k es independientemente 1, 2 ó 3;

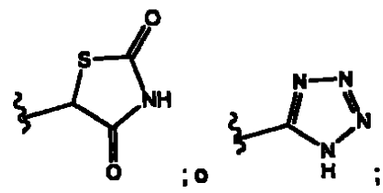
cada m y s son independientemente 0, 1, 2, ó 3;

cada j es 0, 1, o 2;

Cada R^4 es $-(CR^{11}R^{12})_n-$, $-(CR^{11}R^{12})_n-S-(CR^{11}R^{12})_n-$, $-(CR^{11}R^{12})_n-NR^{10}-$, $-(CR^{11}R^{12})_n-NR^{10}-(CR^{11}R^{12})_n-O-$, $-(CR^{11}R^{12})_n-O-(CR^{11}R^{12})_k-NR^{10}$, $-(CR^{11}R^{12})_n-O-(CR^{11}R^{12})_n-$, $-(CR^{11}R^{12})_n-O-(CR^{11}R^{12})_k-O-(CR^{11}R^{12})_n-$, $-(CR^{11}R^{12})_n-CR^{11}=CR^{12}-(CR^{11}R^{12}{}_n-$, o $-CH=CH-(CR^{11}R^{12})-O-(CH_2)_n-$;

Cada R^5 es un enlace o $-(CR^{11}R^{12})_m-Z-(CR^{11}R^{12})_s-$; en el que Z es $-CR^{11}R^{12}-$, $-O-$, $-NR^{10a}-$, o $-(SO)_j-$;

Cada R^6 es $-(C=O)-OH$, $-(C=O)-OM^+$, $-(C=O)-$ alquilo (C_1-C_8), $-(C=O)-O-$ alquilo (C_1-C_8), $-(C=O)-NR^{10}R^{11}$, $-(C=O)-NR^{10}-SO_2-R^{11}$, $-SO_2-NH-R^{10}$, $-NH-SO_2-R^{10}$, $-(C=O)-NH-C\equiv N$, o R^6 tiene una fórmula:



;

M^+ es un catión de metal alcalino o un catión de metal alcalinotérreo;

Cada R^7 y R^8 es independientemente H, alquilo (C_1-C_8), alcoxi (C_1-C_8), $-(CR^{11}R^{12})_t$ cicloalquilo (C_3-C_{10}), $-(CR^{11}R^{12})_t$ arilo (C_6-C_{10}), $-(CR^{11}R^{12})_t$ aril $(C_6-C_{10})-O-$, $-(CR^{11}R^{12})_t$ heterociclilo de (4 – 10) eslabones, o $-(CR^{11}R^{12})_t$ heterociclilo de (4 – 10) eslabones $-O-$;

O R^7 y R^8 pueden opcionalmente tomarse juntos con el carbono al que están unidos para formar un cicloalquilo (C_3-C_{10}) o un heterococlilo de (3 – 10) eslabones;

Cada Ar^1, Ar^2, Ar^3, y Ar^4 representa arilo (C_6-C_{10}) o heterociclilo de (5 – 10) eslabones; en el que los átomos de carbono en el anillo de cada Ar^1, Ar^2,

Ar^3, y Ar^4 están opcionalmente sustituidos con uno a tres grupos R^{13};

El anillo A representa un anillo de 3, 4, 5, 6 ó 7 eslabones conteniendo opcionalmente 1 a 4 heteroátomos que pueden ser el mismo o diferente y que se seleccionan entre $-N(R^{10a})-$, O, y $S(O)_j$, en el que j es 0, 1, ó 2, con la condición de que el anillo no contenga dos átomos de O o $S(O)_j$ adyacentes, y en el que los átomos de carbono del resto A en el anillo estén opcionalmente sustituidos con uno a tres grupos R^{13};

R^9 es alquilo ($C_1 - C_8$), $-(CR^{11}R^{12})_t -$ arilo ($C_8 - C_{10}$) o $(CR^{11}R^{12})_t -$ heterociclilo de (4 – 10) eslabones, en los que t es independientemente 0, 1, 2, 3, 4, ó 5, en el que dichos grupos R^9 están sustituidos con 1 a 3 grupos independientemente seleccionados entre $-(CR^{11}R^{12})_qNR^{10}R^{11}$, $-(CR^{11}R^{12})_qNR^{10}$ alcanoílo ($C_1 - C_6$), $-(CR^{11}R^{12})_qO(CR^{11}R^{12})_rR^{10}$, y $-(CR^{11}R^{12})_qR^{10}$, y en el que los restos heterociclilo, arilo y alquilo de los grupos anteriores están opcionalmente sustituidos con uno a tres grupos R^{13};

R^{9a} y R^{10} son independientemente H o alquilo ($C_1 - C_6$);

R^{11} y R^{12} son independientemente H, alquilo ($C_1 - C_6$), hidroxi, o alcoxi ($C_1 - C_6$);

R^{10a} se selecciona entre H, alquilo ($C_1 - C_6$), $-(C=O)-R^{14}$, $-SO_2NR^{15}R^{16}$, o $-S(O)_j$ alquilo ($C_1 - C_6$);

Cada R^{13} y R^{13a} se seleccionan independientemente entre el grupo constituido por halo, ciano, nitro, trifluorometoxi, trifluorometilo, azido, hidroxi, alcoxi ($C_1 - C_6$), alquilo ($C_1 - C_{10}$), alquenilo ($C_2 - C_6$), alquinilo ($C_2 - C_6$), $-O-(CR^{11}R^{12})_k-O-(CR^{11}R^{12})_n-$, $-(C=O)-R^{14}$, $-(C=O)-O-R^{15}$, $-O-(C=O)-R^{15}$, $-NR^{15}(C=O)-R^{16}$, $-NR^{15}(C=O)-O-R^{16}$, $-(C=O)-NR^{15}R^{16}$, $-NR^{15}R^{16}$, $-NR^{15}OR^{16}$, $-SO_2R^{15}R^{16}$, $-S(O)_j$ alquilo ($C_1 - C_6$), $-O-SO_2-R^{14}$, $-NR^{15}-SO_2-R^{16}$, $R^{15}-$

$(CR^{11}R^{12})_t$ – arilo (C_6 – C_{10}), –$(CR^{11}R^{12})_t$ heterociclilo de (4 – 10) eslabones, –$(CR^{11}R^{12})_q(C=O)(CR^{11}R^{12})_t$ arilo (C_6 – C_{10}), –$(CR^{11}R^{12})_q(C=O)(CR^{11}R^{12})_t$ heterociclilo de (4 – 10) eslabones, –$(CR^{11}R^{12})_tO(CR^{11}R^{12})_q$ arilo (C_6 – C_{10}), –$(CR^{11}R^{12})_tO(CR^{11}R^{12})_q$ heterociclilo de (4 – 10) eslabones, –$(CR^{11}R^{12})_qSO_2(CR^{11}R^{12})_t$ arilo (C_6 – C_{10}), y –$(CR^{11}R^{12})_qSO_2(CR^{11}R^{12})_t$ heterociclilo de (4 – 10) eslabones; 1 ó 2 átomos de carbono en el anillo de los restos heterocíclicos de los grupos anteriores R^{13} y R^{13a} están opcionalmente sustituidos con un resto oxo (=O), y los restos alquilo, alquenilo, alquinilo, arilo y heterocíclicos de los grupos anteriores R^{13} y R^{13a} están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente entre halo, ciano, nitro, trifluorometilo, trifluorometoxi, azido, –OR^{15}, –(C=O)–R^{15}, –(C=O)–O–R^{15}, –O–(C=O)–R^{15}, –NR^{15}(C=O)–R^{16}, –(C=O)–$NR^{15}R^{16}$, –$NR^{15}R^{16}$, –$NR^{15}OR^{16}$, alquilo (C_1 – C_6), alquenilo (C_2 – C_6), alquinilo (C_2 – C_6), –$(CR^{11}R^{12})_t$ arilo (C_6 – C_{10}), y –$(CR^{11}R^{12})_t$ heterociclilo de (4 – 10) eslabones;

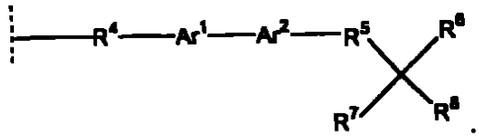
cada R^{14}, R^{15}, y R^{16} se selecciona independientemente entre H, alquilo (C_1 – C_6), –$(CR^{11}R^{12})_t$ arilo (C_6 – C_{10}) y –$(CR^{11}R^{12})_t$ heterociclilo de (4 – 10) eslabones; 1 ó 2 átomos de carbono en el anillo del grupo heterocíclico están opcionalmente sustituidos con un resto oxo (=O), y los retos, alquilo, arilo y heterocíclico de los grupos anteriores R^{14}, R^{15} y R^{16} están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente entre halo, ciano, nitro, –$NR^{11}R^{12}$, trifluorometilo, trifluorometoxi, alquilo (C_1 – C_6), alquenilo (C_2 – C_6), alquinilo (C_2 – C_6), hidroxi, y alcoxi (C_1 – C_6);

R^{17} es H, alquilo (C_1 – C_6), –O– alquilo (C_1 – C_6), halo, CN, OH, CF_3, u –O–CF_3;

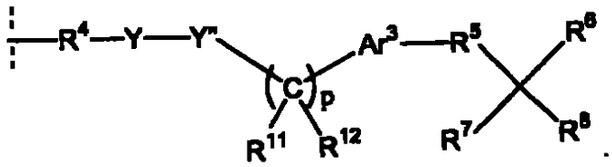
y en el que cualquiera de los sustituyentes anteriormente mencionados

comprende un grupo CH_3 (metilo), CH_2 (metileno), o CH (metino) que no está unido a un grupo halo, SO o SO_2 o a un átomo N, O o S opcionalmente se soporta sobre dicho grupo un sustituyente seleccionado entre hidroxi, halo, alquilo ($C_1 - C_4$), alcoxi ($C_1 - C_4$), $-NH_2$, –NH alquilo ($C_1 - C_8$), y –N (alquilo ($C_1 - C_8$))$_2$.

En una realización, la invención se refiere a los compuestos de fórmula I en la que R^3 es

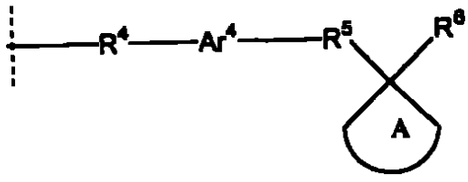
A) 

En otra realización, la invención se refiere a los compuestos de fórmula I en la que R^3 es

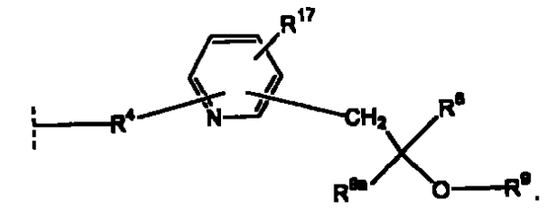
B) 

Dentro de esta realización, los restos $-R^4-Y-Y''-$ preferidos son $-(CR^{11}R^{12})_n-O-(CR^{11}R^{12})_n-(C=O)-NR^{10}$ o $-(CR^{11}R^{12})_n-NR^{10}-(C=O)-O-$.

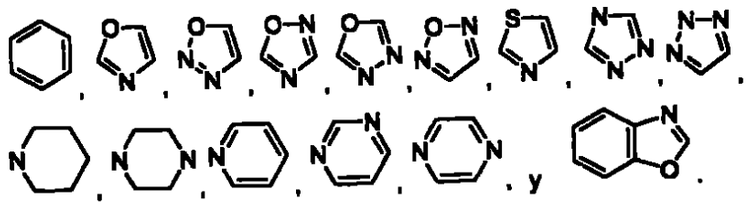
En otra realización, la invención se refiere a los compuestos de fórmula I en la que R^3 es

C) 

En otra realización, la invención se refiere a los compuestos de fórmula I en la que R^3 es

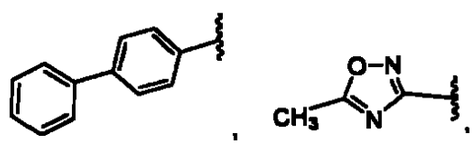
D) 

En otra realización, la invención se refiere a los compuestos de fórmula I en la que el anillo Q se selecciona entre el grupo constituido por

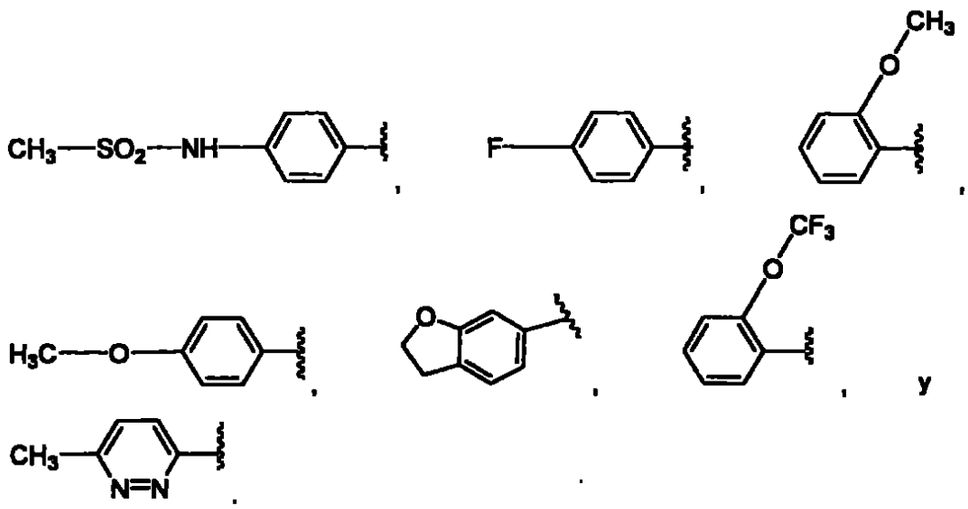


En otra realización, la invención se refiere a los compuestos de fórmula I en la que R^1 es H, halo, alquilo ($C_1 - C_8$), alcoxi ($C_1 - C_8$), CF_3, -O-CF_3, -O-SO_2-alquilo ($C_1 - C_8$), –O-SO_2– $(CR^{11}R^{12})_t$ arilo ($C_6 - C_{10}$), o –$(CR^{11}R^{12})_t$ aril ($C_6 - C_{10}$) –O–, en los que los átomos de carbono en el anillo de R^1 están opcionalmente sustituidos con 1 a 3 grupos R^{13}.

En otra realización, la invención se refiere a los compuestos de fórmula I

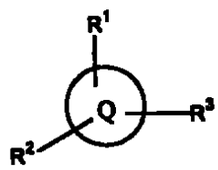


en la que R^2 es H, fenilo,

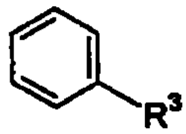
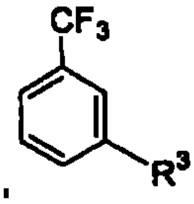
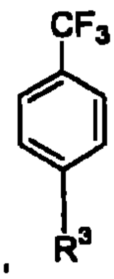
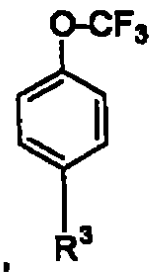
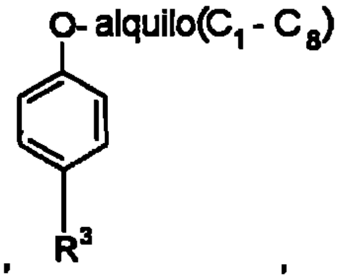


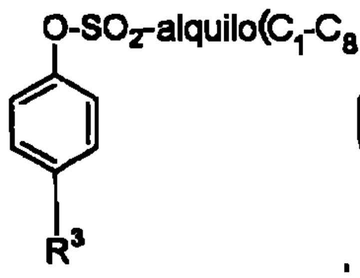
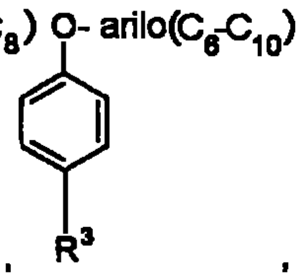
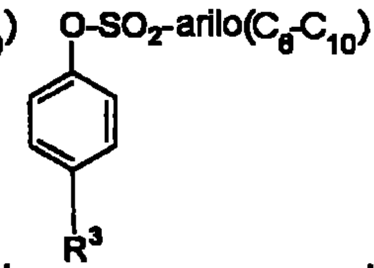
y

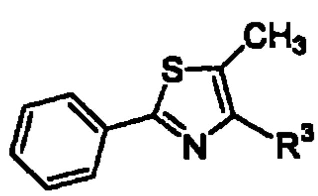
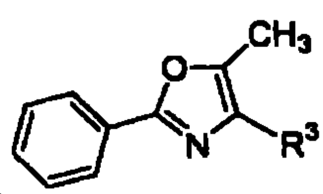
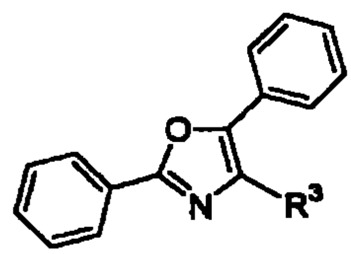
En otra realización, la invención se refiere a los compuestos de fórmula I

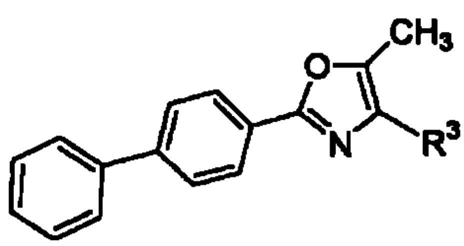
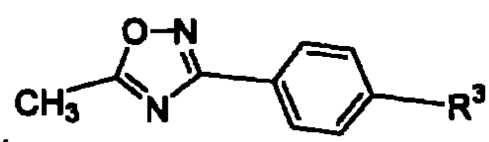


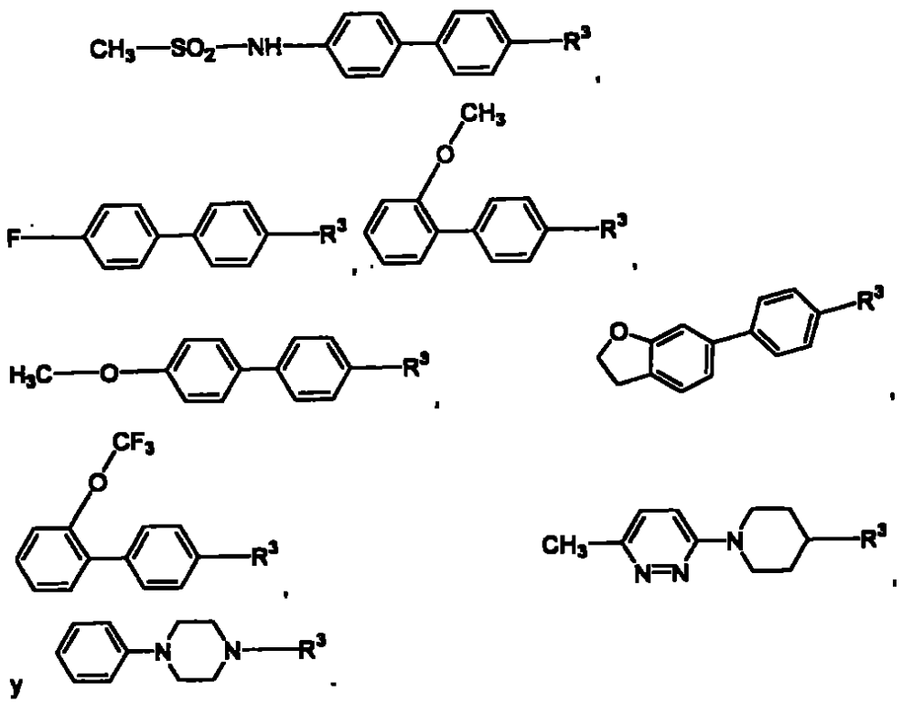
en la que dicho se selecciona entre el grupo constituido por:


R3
,

CF3
R3
,

CF3
R3
,

O-CF3
R3
,

O- alquilo(C1 - C8)
R3
,


O-SO2-alquilo(C1-C8)
R3
,

O- arilo(C6-C10)
R3
,

O-SO2-arilo(C6-C10)
R3
,


CH3
S
N
R3
,

CH3
O
N
R3
,

O
N
R3
,


CH3
O
N
R3
,

O-N
CH3
N
R3
,



y

En otra realización, la invención se refiere a los compuestos de fórmula I en la que R^4 es $-CH_2-O-$, $-CH_2-O-CH_2-$, $-CH_2-CH_2-O-$, $-CH=CH-CH_2-O-$, o $-CH_2-CH_2-CH_2-O-$.

En otra realización, la invención se refiere a los compuestos de fórmula I en la que R^4 es $-(CH)_n-$, en la que n es independientemente 0, 1, 2 ó 3.

En otra realización, la invención se refiere a los compuestos de fórmula I en la que R^5 es un enlace o $-(CR^{11}R^{12})_m-Z-(CR^{11}R^{12})_s$; en el que Z es $-O-$, $-NR^{10a}-$, o $-S(O)_j-$, en los que cada m y s son independientemente 0, 1, 2, ó 3; en los que j es 0, 1, ó 2.

En otra realización, la invención se refiere a los compuestos de fórmula I en la que R^5 es un enlace, $-O-$, $-CH_2-$, $-C(CH_3)H-$, $-C(OH)H-$, o $-C(O-$ alquilo $(C_1-C_8))H-$.

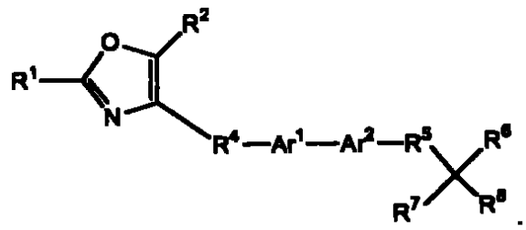
En otra realización, la invención se refiere a los compuestos de fórmula I en la que R^6 es –(C=O)-OH.

En otra realización, la invención se refiere a los compuestos de fórmula I en la que R^6 es $-(C=O)-OM^+$, en el que M^+ se selecciona entre el grupo constituido por Ca^{++}, Li^+, Na^+ y K^+.

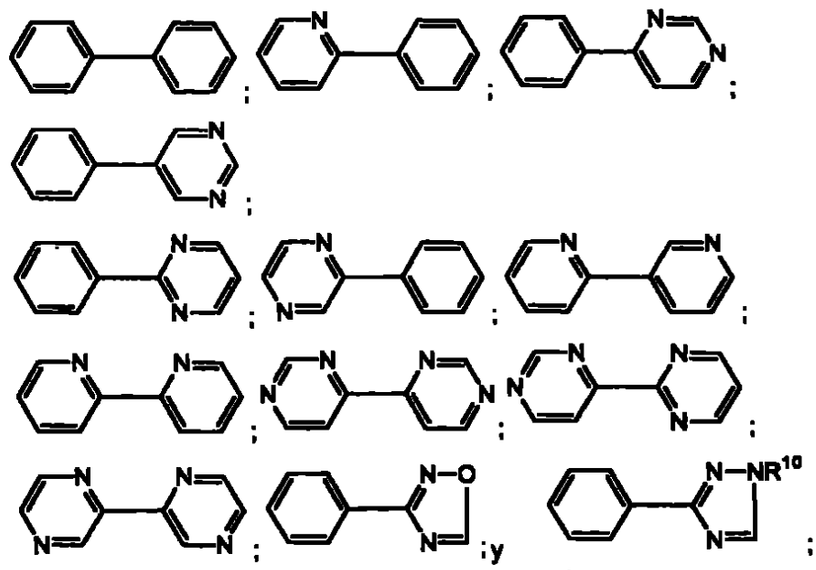
En otra realización, la invención se refiere a los compuestos de fórmula I en la que cada R^7 y R^8 es independientemente H, alquilo ($C_1 - C_8$) o alcoxi ($C_1 - C_8$).

En otra realización, la invención se refiere a los compuestos de fórmula I en la que cada R^7 y R^8 se toman junto con el carbono al que se unen para formar un heterociclilo de (3 – 7) eslabones.

En otra realización, la invención se refiere a los compuestos que tienen una fórmula:

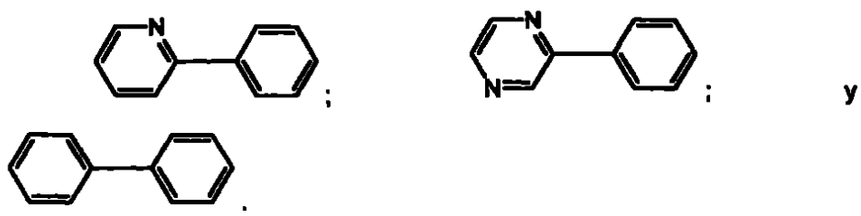


En esta realización, la invención se refiere a los compuestos en los que dicho $-Ar^1-Ar^2-$ se selecciona entre el grupo constituido por:



en las que los átomos de carbono en el anillo de cada Ar^1 y Ar^2 están opcionalmente sustituidos con 1 a 3 grupos R^{13} seleccionados entre el grupo constituido por halo, alquilo ($C_1 - C_8$) y alcoxi ($C_1 - C_8$).

Preferiblemente, dicho–Ar^1-Ar^2- se selecciona entre el grupo constituido por:



En esta realización, los compuestos específicos de la presente invención se seleccionan entre el grupo constituido por

Ácido 2-metil-2-({3'-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]-1,1'-bifenil-3-il}oxi)propanoico;

Ácido 2-metil-2-[(3'-{[4-trifluorometil)bencil]oxi}-1,1'-bifenil-3-il}oxi]propanoico;

Ácido 2-metil-2-[(3'-{2-[1-(6-metilpiridazin-3-il)piperidin-4-il]etoxi}-1,1'-bifenil-3-il)oxi]propanoico;

Ácido 1-({3'-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]-1,1'-bifenil-3-il}oxi)ciclobutanocarboxílico;

Ácido 2-({3'-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]-1,1'-bifenil-3-il}oxi)butanoico;

Ácido 2-(3-{6-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridin-2-il}fenoxi)butanoico;

Ácido 1-(3-{6-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridin-2-il}fenoxi) ciclobutanocarboxílico;

Ácido 2-metil-2-(3-{6-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridin-2-il}fenoxi)propanoico;

Ácido 2-metil-2-(3-{6-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]pirazin-2-il}fenoxi)propanoico; y

las sales farmacéuticamente aceptables de los mismos.

Dentro de esta realización, un compuesto específico de la presente invención es ácido 1-({3'-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]-1,1'-bifenil-3-il}oxi)ciclobutanocarboxílico o las sales farmacéuticamente aceptables del mismo.

Dentro de esta realización, un compuesto específico de la presente invención es ácido 2-({3'-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]-1,1'-bifenil-3-il}oxi)butanoico o las sales farmacéuticamente aceptables del mismo.

Dentro de esta realización, un compuesto específico de la presente

invención es ácido 2-(3-{6-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridin-2-il}fenoxi)butanoico o las sales farmacéuticamente aceptables del mismo.

Dentro de esta realización, un compuesto específico de la presente invención es ácido 1-(3-{6-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridin-2-il}fenoxi)ciclobutanocarboxílico o las sales farmacéuticamente aceptables del mismo.

Dentro de esta realización, un compuesto específico de la presente invención es ácido 1-[(3'-{[2-(3-fluorofenil)-5-metil-1,3-oxazol-4-il]metoxi}bifenil-3-il)oxi]ciclobutanocarboxílico o las sales farmacéuticamente aceptables del mismo.

Dentro de esta realización, un compuesto específico de la presente invención es ácido 1-({3'-[3-(5-metil-2-fenil-1,3-oxazol-4-il)propoxi]bifenil-3-il}oxi) ciclobutanocarboxílico o las sales farmacéuticamente aceptables del mismo.

Dentro de esta realización, un compuesto específico de la presente invención es ácido 1-[(3'-{[5-(4-metoxifenil)-1,2,4-oxadiazol-3-il]metoxi}bifenil-3-il)oxi]ciclobutanocarboxílico o las sales farmacéuticamente aceptables del mismo.

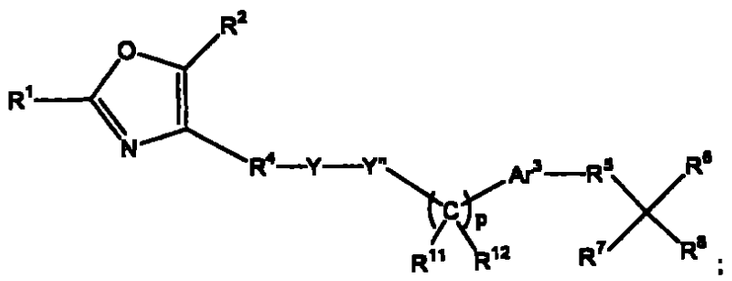
Dentro de esta realización, un compuesto específico de la presente invención es ácido 2-[(3'-{2-[2-(3-fluorofenil)-5-metil-1,3-oxazol-4- il]etoxi}bifenil-3-il)oxi]-2-metilpropanoico o las sales farmacéuticamente aceptables del mismo.

Dentro de esta realización, un compuesto específico de la presente invención es ácido 2-metil-2-({3'-[(5-metil-2-fenil-1,3-oxadiazol-4-il)metoxi]bifenil-3-il}oxi)propanoico o las sales farmacéuticamente aceptables

del mismo.

Dentro de esta realización, un compuesto específico de la presente invención es ácido 2-etoxi-3-{3'-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]bifenil-3-il}propanoico o las sales farmacéuticamente aceptables del mismo.

En otra realización, la invención se refiere a los compuestos que tienen una fórmula:



en la que Y es –(C=O) – o $-SO_2-$; Y'' es NR^{10} y p es 1.

Preferiblemente, cada R^{11} y R^{12} son independientemente H.

Preferiblemente Ar^3 es fenilo.

En esta realización, los compuestos específicos de la presente invención se seleccionan entre el grupo constituido por:

Ácido 1-(3-{[({2-[3-(trifluorometil)fenil]etoxi}carbonil)amino]metil}fenoxi) ciclobutanocarboxílico;

Ácido 2-(3-{[({2-[3-(trifluorometil)fenil]etoxi}carbonil)amino]metil}fenoxi) butanoico;

Ácido 2-metil-2-(3-{[({2-[3-(trifluorometil)fenil]etoxi}carbonil)amino]metil}fenoxi)propanoico;

Ácido 2-metil-2-(3-{[({2-[5-metil-2-fenil-1,3-oxazol-4-il]etoxi}carbonil}amino]metil}fenoxi)propanoico;

Ácido 2-metil-2-(3-{[({[4-(5-metil-1,2,4-oxadiazol-3-

il)benci]oxi}carbonil)amino]metil}fenoxi)propanoico;

Ácido 2-{3-[({[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]carbonil}amino)metil]fenoxi}butanoico;

Ácido 1-{3-[({[2-[5-metil-2-fenil-1,3-oxazol-4-il]etoxi]carbonil}amino)metil]fenoxi}ciclobutanocarboxílico;

Ácido 1-{3-[({[3-[5-metil-2-fenil-1,3-oxazol-4-il]propoxi]carbonil}amino)metil]fenoxi}ciclobutanocarboxílico;

Ácido 2-{3-[({[3-[5-metil-2-fenil-1,3-oxazol-4-il]propoxi]carbonil}amino)metil]fenoxi}butanoico;

Ácido 2-metil-2-{3-[({[3-[5-metil-2-fenil-1,3-oxazol-4-il]propoxi]carbonil}amino)metil]fenoxi}propanoico;

y las sales farmacéuticamente aceptables de los mismos.

En esta realización, un compuesto específico de la presente invención es ácido 2-metil-2-{3-[({2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]carbonil}amino)metil]fenoxi}propanoico o las sales farmacéuticamente aceptable del mismo.

En esta realización, un compuesto específico de la presente invención es ácido 2-metil-2-(3-[({[(5-metil-2-fenil-1,3-oxazol-4-il)metoxi]carbonil}amino)metil]fenoxi}propanoico o las sales farmacéuticamente aceptable del mismo.

En esta realización, un compuesto específico de la presente invención es ácido 2-metil-2-{4-[({[3-(5-metil-2-fenil-1,3-oxazol-4-il)propoxi]carbonil}amino)metil]fenoxi}propanoico o las sales farmacéuticamente aceptable del mismo.

En esta realización, un compuesto específico de la presente invención

es ácido 2-{3-fluoro-4-[({[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]carbonil}amino)metil]fenoxi}-2-metilpropanoico o las sales farmacéuticamente aceptable del mismo.

En esta realización, un compuesto específico de la presente invención es ácido 2-{3-[({[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]carbonil}amino)metil]fenoxi}butanoico o las sales farmacéuticamente aceptable del mismo.

En esta realización, un compuesto específico de la presente invención es ácido 2-{3-[({[(5-metil-2-fenil-1,3-oxazol-4-il)metoxi]carbonil}amino)metil]fenoxi}butanoico o las sales farmacéuticamente aceptable del mismo.

En esta realización, un compuesto específico de la presente invención es ácido 1-{3-[({[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]carbonil}amino)metil]fenoxi} ciclobutanocarboxílico o las sales farmacéuticamente aceptable del mismo.

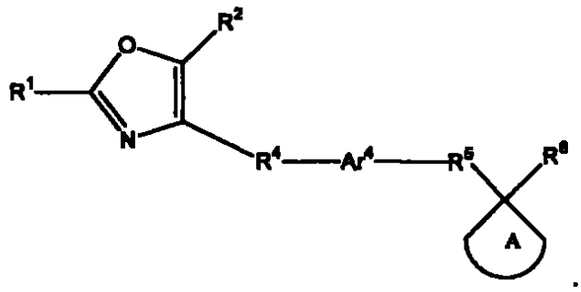
En esta realización, un compuesto específico de la presente invención es ácido 2-metil-2-(3-{[({[2-(5-metil-2-fenil-1,3-oxazol-4-il)etil]amino}carbonil)oxi]metil}fenoxi)propanoico o las sales farmacéuticamente aceptable del mismo.

En esta realización, un compuesto específico de la presente invención es ácido 2-etoxi-3-{3-[({[3-(5-metil-2-fenil-1,3-oxazol-4-il)propoxi]cabonil}amino)metil]fenil}propanoico o las sales farmacéuticamente aceptable del mismo.

En esta realización, un compuesto específico de la presente invención es ácido 2-etoxi-3-{3-[({[2-(5-metil-2-fenil-1,3-oxazol-4-

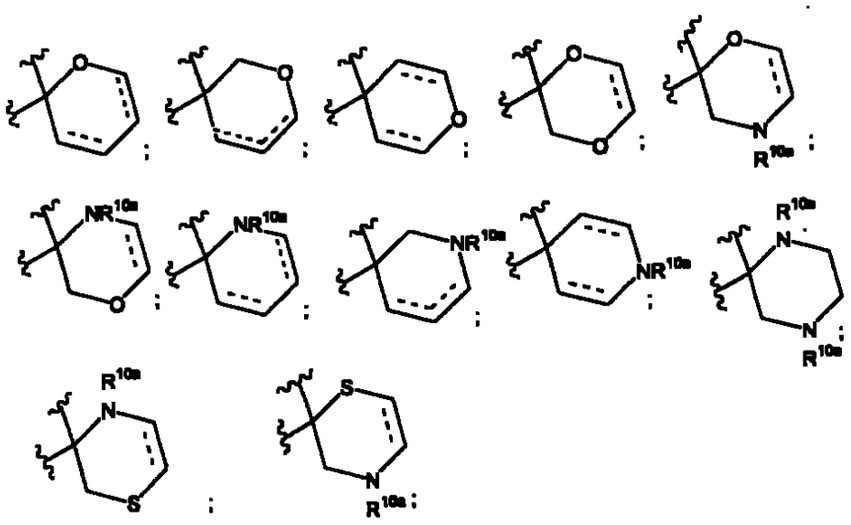
il)etoxi]caboníl}amino)metil}fenil} propanoico o las sales farmacéuticamente aceptable del mismo.

En otra realización, la invención se refiere a los compuestos que tienen una fórmula:



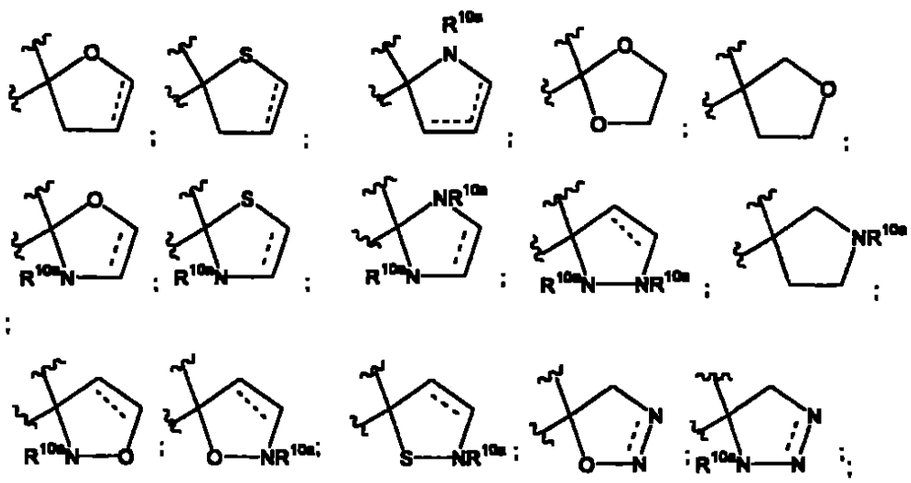
En otra realización, el anillo A se selecciona entre el grupo constituido por ciclopropilo, ciclobutilo, ciclopentilo y ciclohexilo.

En otra realización, el anillo A se selecciona entre el grupo constituido por



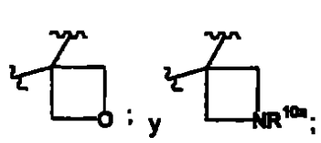
en las que — es un doble enlace opcional.

En otra realización, el anillo A se selecciona entre el grupo constituido por



en las que — es un doble enlace opcional.

En otra realización, el anillo A se selecciona entre el grupo constituido por



en las que — es un doble enlace opcional.

En otra realización, Ar^4 es fenilo, naftilo, piridinilo, pirimidinilo, o pirazinilo.

En esta realización, los compuestos específicos de la presente invención se seleccionan entre el grupo constituido por

Ácido 1-{4-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]bencil}ciclohexanocarboxílico;

Ácido 1-{4-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]bencil}ciclopentanocarboxílico;

Ácido 1-{4-[3-(5-metil-2-fenil-1,3-oxazol-4-il)propoxi]bencil}ciclopentanocarboxílico;

Ácido 4-{4-[(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]bencil}tetrahidro-2H-piran-4-carboxílico;

Ácido 4-{4-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]bencil}tetrahidro-2H-piran-4-carboxílico;

Ácido 1-{4-[2-(4'-metoxi-1,1'-bifenil-4-il)etoxi]bencil}ciclobutanocarboxílico;

Ácido 1-{4-[2-(4'-fluoro-1,1'-bifenil-4-il)etoxi]bencil}ciclobutanocarboxílico;

Ácido 1-{4-[2-(2'-metoxi-1,1'-bifenil-4-il)etoxi]bencil}ciclobutanocarboxílico;

Ácido 1-{4-[2-(3'-(trifluorometoxi)-1,1'-bifenil-4-il)etoxi]bencil}ciclobutanocarboxílico;

Ácido 1-(4-{2-[4-(6-metoxipiridin-3-il)fenil]etoxi}bencil)ciclobutanocarboxílico;

Ácido 1-(4-{2-[4'-(metilsulfonil)-1,1'-bifenil-4-il]etoxi}bencil)ciclobutanocarboxílico;

Ácido 1-(4-{2-(4-(2,3—dihidro-1-benzofuran-6-il)fenil]etoxi}bencil)ciclobutanocarboxílico;

Ácido 1-[4-(2-{4'-[(metilsulfonil)amino]-1,1'-bifenil-4-il}etoxi)bencil]ciclobutanocarboxílico;

Ácido 1-{4-[3-(5-metil-2-fenil-1,3-oxazol-4-il)propoxi]bencil}ciclobutanocarboxílico;

Ácido 1-{4-[(5-metil-2-fenil-1,3-oxazol-4-il)metoxi]bencil}ciclobutanocarboxílico;

Ácido 1-{3-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]bencil}ciclobutanocarboxílico;

Ácido 1-{4-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]bencil}ciclobutanocarboxílico;

Ácido 1-{4-[(2,5-difenil-1,3-oxazol-4-il)metoxi]bencil}ciclobutanocarboxílico;

Ácido 1-{4-[3-(2,5-difenil-1,3-oxazol-4-il)propoxi]bencil}ciclobutanocarboxílico;

Ácido 1-{4-[(2,5-difenil-1,3-oxazol-4-il)metoxi]fenoxi}ciclobutanocarboxílico;

Ácido 1-{4-[3-(2,5-difenil-1,3-oxazol-4-il)propoxi]fenoxi}ciclobutanocarboxílico;

Ácido 1-(4-{2-[2-(1,1'-bifenil-4-il)-5-metil-1,3-oxazol-4-il)etoxi}fenoxi)ciclobutanocarboxílico;

Ácido 1-{4-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]fenoxi}ciclobutanocarboxílico;

Ácido 1-{4-[3-(5-metil-2-fenil-1,3-oxazol-4-il)propoxi]fenoxi}ciclobutanocarboxílico;

Ácido 1-{4-[(5-metil-2-fenil-1,3-oxazol-4-il)metoxi]fenoxi}ciclobutanocarboxílico;

Ácido 1-({6-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridin-3-

il}metil)ciclobutanocarboxílico;

Ácido 1-(hidroxi-{6-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridin-3-il}metil)ciclobutanocarboxílico;

Ácido 1-({6-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridin-3-il}metil)ciclopentanocarboxílico;

Ácido 1-({6-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridin-3-il}metil)ciclohexanocarboxílico;

Ácido 2-({6-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridin-3-il}metil)tetrahidrofuran-2-carboxílico;

Ácido 2-({5-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridin-2-il}metil)tetrahidrofuran-2-carboxílico;

y las sales farmacéuticamente aceptables de los mismos.

En esta realización, un compuesto específico de la presente invención es ácido 1-{4-[3-(5-metil-2-fenil-1,3-oxazol-4-il)propoxi]bencil}ciclobutanocarboxílico o las sales farmacéuticamente aceptable del mismo.

En esta realización, un compuesto específico de la presente invención es ácido 1-{4-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]bencil}ciclobutanocarboxílico o las sales farmacéuticamente aceptable del mismo.

En esta realización, un compuesto específico de la presente invención es ácido 2-({6-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridin-3-il}metil)tetrahidrofuran-2-carboxílico o las sales farmacéuticamente aceptable del mismo.

En esta realización, un compuesto específico de la presente invención

es ácido 2-({5-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridin-2-il}metil)tetrahidrofuran-2-carboxílico o las sales farmacéuticamente aceptable del mismo.

En esta realización, un compuesto específico de la presente invención es ácido 2-({6-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridin-3-il}metil)tetrahidro-2*H*-piran-2-carboxílico o las sales farmacéuticamente aceptable del mismo.

En esta realización, un compuesto específico de la presente invención es ácido 2-[(6-{2-[2-(3-clorofenil)-5-metil-1,3-oxazol-4- il]etoxi}piridin-3-il)metil]tetrahidrofuran-2-carboxílico o las sales farmacéuticamente aceptable del mismo.

En esta realización, un compuesto específico de la presente invención es ácido 2-[(6-{2-[2-(3-metoxifenil)-5-metil-1,3-oxazol-4-il]etoxi}piridin-3-il)metil]tetrahidrofuran-2-carboxílico o las sales farmacéuticamente aceptable del mismo.

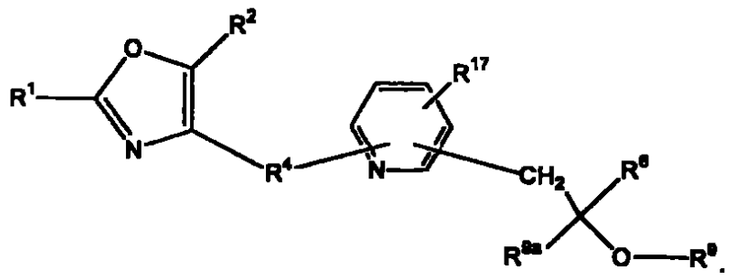
En esta realización, un compuesto específico de la presente invención es ácido 2-{5-[2-(5-metil-2-feniloxazol-4-il)etoxi]pirazin-2-ilmetil}tetrahidrofuran-2- carboxílico o las sales farmacéuticamente aceptable del mismo.

En esta realización, un compuesto específico de la presente invención es ácido -{4-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]bencil}tetrahidrofuran-2-carboxílico o las sales farmacéuticamente aceptable del mismo.

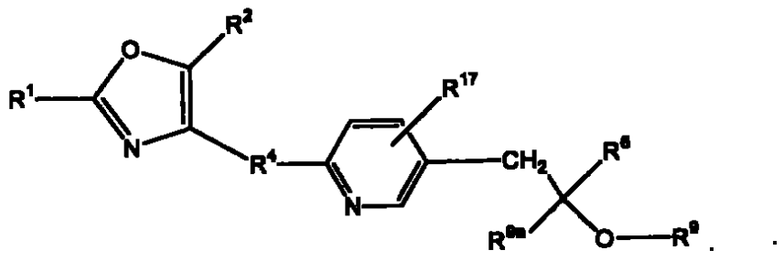
En esta realización, un compuesto específico de la presente invención es ácido 2-{6-[2-(5-metil-2-fenil-oxazol-4- il)etoxi]naftalen-2-ilmetil}tetrahidrofuran-2-carboxílico o las sales farmacéuticamente aceptable del mismo.

En otra realización, la invención se refierè a los compuestos que tienen

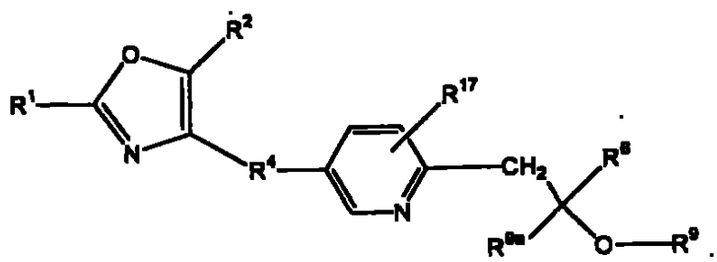
una fórmula:



En esta realización, preferiblemente la invención se refiere a los compuestos que tienen la fórmula:



En esta realización, preferiblemente la invención se refiere a los compuestos que tienen la fórmula:



En esta realización, preferiblemente R^9 es metilo, etilo o bencilo. Preferiblemente R^{17} es H.

En esta realización, un compuesto específico de la presente invención es ácido 2-etoxi-3-{6-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridin-3-il}propanoico o las sales farmacéuticamente aceptable del mismo.

En esta realización, un compuesto específico de la presente invención es ácido 2-metoxi-3-(6-{2-[5-metil-2-(3-metilfenil)-1,3-oxazol-4-il]etoxi}piridin-3-il)propanoico o las sales farmacéuticamente aceptable del mismo.

En esta realización, un compuesto específico de la presente invención es ácido 2-metoxi-3-{6-[2-(4-fenoxifenil)etoxi]piridin-3-il}propanoico o las sales farmacéuticamente aceptable del mismo.

En esta realización, un compuesto específico de la presente invención es ácido 2-etoxi-3-[6-(2-{4-[(fenilsulfonil)oxi]fenil}etoxi)piridin-3-il]propanoico o las sales farmacéuticamente aceptable del mismo.

En esta realización, un compuesto específico de la presente invención es ácido 2-etoxi-3-{5-[2-(5-metil-2-feniloxazol-4-il)etoxi]piridin-2-il}propiónico o las sales farmacéuticamente aceptable del mismo.

En esta realización, un compuesto específico de la presente invención es ácido 2-metoxi-2-metil-3-{6-[3-(5-metil-2-feniloxazol-4-il)propoxi]piridin-3-il}propiónico o las sales farmacéuticamente aceptable del mismo.

En esta realización, un compuesto específico de la presente invención es ácido 2-metoxi-2-metil-3-{5-[2-(5-metil-2-feniloxazol-4-il)etoxi]piridin-2-il}propiónico o las sales farmacéuticamente aceptable del mismo.

En esta realización, un compuesto específico de la presente invención

es ácido 3-(6-{2-[2-(4-clorofenil)-5-metiloxazol-4-il]etoxi}piridin-3-il)-2-metoxi-2-metilpropiónico o las sales farmacéuticamente aceptable del mismo.

En esta realización, un compuesto específico de la presente invención es ácido 2-metoxi-2-metil-3-{6-[2-(5-metil-2-feniloxazol-4-il)etoxi]piridin-3-il}propiónico o las sales farmacéuticamente aceptable del mismo.

En esta realización, un compuesto específico de la presente invención es ácido 2-metoxi-3-(6-{2-[2-(3-metoxifenil)-5-metiloxazol-4-il]etoxi}piridin-3- il)-2-metilpropiónico o las sales farmacéuticamente aceptable del mismo.

La presente invención también proporciona un procedimiento de tratamiento de diabetes mellitus no insulinodependiente en un mamífero comprendiendo la administración al mamífero en necesidad del mismo de una cantidad terapéuticamente eficaz de un compuesto de fórmula (I). En una realización, dicho mamífero tiene una tolerancia a la glucosa alterada.

La presente invención también proporciona un procedimiento de tratamiento de síndrome de ovario poliquístico en un mamífero comprendiendo la administración al mamífero en necesidad del mismo de una cantidad terapéuticamente eficaz de un compuesto de fórmula (I).

La presente invención también proporciona un procedimiento de tratamiento de obesidad en un mamífero comprendiendo la administración al mamífero en necesidad del mismo de una cantidad terapéuticamente eficaz de un compuesto de fórmula (I).

La presente invención también proporciona un procedimiento de tratamiento de reducción de peso corporal en un mamífero obeso comprendiendo la administración al mamífero en necesidad del mismo de una cantidad terapéuticamente eficaz de un compuesto de fórmula (I).

La presente invención también proporciona un procedimiento de tratamiento de hiperglucemia en un mamífero comprendiendo la administración al mamífero en necesidad del mismo de una cantidad terapéuticamente eficaz de un compuesto de fórmula (I).

La presente invención también proporciona un procedimiento de tratamiento de hiperlipidemia en un mamífero comprendiendo la administración al mamífero en necesidad del mismo de una cantidad terapéuticamente eficaz de un compuesto de fórmula (I).

La presente invención también proporciona un procedimiento de tratamiento de hipercolesterolemia en un mamífero comprendiendo la administración al mamífero en necesidad del mismo de una cantidad terapéuticamente eficaz de un compuesto de fórmula (I).

La presente invención también proporciona un procedimiento de tratamiento de aterosclerosis en un mamífero comprendiendo la administración al mamífero en necesidad del mismo de una cantidad terapéuticamente eficaz de un compuesto de fórmula (I).

La presente invención también proporciona un procedimiento de tratamiento de hipertrigliceridemia en un mamífero comprendiendo la administración al mamífero en necesidad del mismo de una cantidad terapéuticamente eficaz de un compuesto de fórmula (I).

La presente invención también proporciona un procedimiento de tratamiento de hiperinsulinemia en un mamífero comprendiendo la administración al mamífero en necesidad del mismo de una cantidad terapéuticamente eficaz de un compuesto de fórmula (I).

La presente invención también proporciona un procedimiento de

tratamiento de un paciente que padece de trastornos de insulina y/o indicios de glucosa anormales asociados a glucocorticoides circulantes, hormona de crecimiento, catecolaminas, glucagón, u hormona paratiroidea, comprendiendo la administración a dicho paciente de una cantidad terapéuticamente eficaz de un compuesto de fórmula (I).

La presente invención también proporciona un procedimiento de tratamiento de resistencia a la insulina en seres humanos comprendiendo la administración a un paciente en necesidad de tratamiento de una cantidad terapéuticamente eficaz de un compuesto de fórmula (I).

La presente invención también proporciona un procedimiento de tratamiento de trastornos relativos a PPAR en seres humanos comprendiendo la administración a un paciente en necesidad de tratamiento de una cantidad terapéuticamente eficaz de un compuesto de fórmula (I).

La presente invención también proporciona un procedimiento de modulación de la actividad PPAR en un mamífero, comprendiendo la administración a un mamífero de una cantidad terapéuticamente eficaz de un compuesto de fórmula (I).

La presente invención también proporciona un procedimiento de reducción de la glucosa en sangre en un mamífero, comprendiendo la administración a un mamífero de una cantidad de un compuesto de fórmula (I) eficaz para reducir los niveles de glucosa en sangre.

La presente invención también proporciona un procedimiento de modulación de la diferenciación de células de grasa en un mamífero, comprendiendo la administración a un mamífero de una cantidad terapéuticamente eficaz de un compuesto de fórmula (I).

La presente invención también proporciona un procedimiento de modulación de los procesos mediados por PPAR en un mamífero, comprendiendo la administración a un mamífero de una cantidad terapéuticamente eficaz de un compuesto de fórmula (I).

La presente invención también proporciona un procedimiento de incremento de la sensibilidad a la insulina en mamíferos, comprendiendo la administración a un mamífero de una cantidad terapéuticamente eficaz de un compuesto de fórmula (I).

La presente invención también proporciona un procedimiento de tratamiento de síndromes metabólicos seleccionados entre el grupo constituido por galactosemia, enfermedad de orina en jarabe de arce, fenilcetonuria, hipersarcosinemia, timina uraciluria, sulfinuria, acidemia isovalérica, sacaropinuria, aciduria 4-hidroxibutírica, deficiencia de la glucosa-6-fosfatodeshidrogenasa, y deficiencia de la piruvatodeshidrogenasa.

La presente invención también proporciona una composición que comprende al menos un modulador de PPAR de fórmula (I) y un vehículo farmacéuticamente aceptable del mismo. Los vehículos farmacéuticamente aceptables ejemplares incluyen vehículos adecuados para administración oral, intravenosa, subcutánea, intramuscular, intracutánea y similares. Se contempla la administración en forma de cremas, lociones, comprimidos, polvos dispersables, gránulos, elixires, soluciones, suspensiones o emulsiones acuosas o no acuosas estériles, y similares.

Los agonistas PPAR de la presente invención se pueden administrar en combinación con otros agentes tales como inhibidores de la α-glucosidasa, inhibidores de la aldosarreductasa, preparaciones de de biguanidina,

compuestos a base de estatina, inhibidores de la síntesis de escualeno, compuestos a base de fibratos, promotores del catabolismo de LDL e inhibidores de la enzima conversora de la angiotensina.

En la descripción anterior, un inhibidor de la α-glucosidasa es un medicamento que tiene acción en la inhibición de una enzima digestiva tal como la amilasa, maltasa, α-dextrinasa o sacarasa, por lo tanto retardando la digestión de almidón o sacarosa. Los ejemplos de los inhibidores de la α-glucosidasa incluyen acarbosa, N-(1,3-dihidroxi-2-propil)variolamina (nombre común: voglibosa) y miglitol.

En la descripción anterior, un inhibidor de la aldosarreductasa es un medicamento que inhibe una enzima limitante de la velocidad de la etapa primera de la vía de del poliol, por lo tanto inhibiendo las complicaciones diabéticas. Los ejemplos incluyen tolrestat, epalrestat, 2,7-difluoroespiro (9H-fluoren-9,4'-imidazolidina)-2',5'-diona (nombre común: imirestat), ácido 3-[(4-bromo-2-fluorofenil)metil]-7-cloro-3,4-dihidro-2,4-dihidro-2,4-dioxo-1(2H)-quinozolinacético (nombre común: zenarestat), 6-fluoro-2,3-dihidro-2,5'-dioxo-espiro[4H-1-benzopiran-4,4'-imidazolidina]-2-carboxamiida (SNK-860), zopolrestat, sorbinil y 1-[(3-bromo-2-benzofuranil)sulfonil]-2,4-imidazolidinadiona (M-16209).

En la descripción anterior, una preparación de biguanida es un medicamento que tiene efectos en la promoción de la glucólisis anaerobia, refuerzo de acción de insulina en la periferia, inhibición de la absorción de glucosa intestinal, inhibición de la gluconeogénesis hepática e inhibición de la oxidación de ácidos grasos y los ejemplos incluyen fenformina, metformina y buformina.

En la anterior descripción, un compuesto a base de estatina es un medicamento que inhibe la hidroximetilglutaril CoA (abreviadamente en inglés HMG-CoA) reductasa, por lo tanto reduciendo el nivel de colesterol en sangre y los ejemplos incluyen pravastatina y la sal sódica de la misma, simvastattina, lovastatina, atorvastatina y fluvastataina.

En la descripción anterior, un inhibidor de la síntesis de escualeno es un medicamento que inhibe la síntesis de escualeno, reduciendo por lo tanto el nivel de colesterol en sangre y los ejemplos incluyen (S)-α-[bis(2,2-dimetil-1-oxopropoxi)metoxi]fosfinil-3-fenoxibencenobutanosulfonato de monopotasio (BMS 188494).

En la descripción anterior, un compuesto a base de fibratos es un medicamento para inhibir la síntesis y secreción de triglicéridos en el hígado y activar la lipoproteínalipasa, por lo tanto reduciendo el nivel de triglicéridos en la sangre. Los ejemplos incluyen bezafibrato, beclobrato, binifibrato, ciprofibrato, clinofibrato, clofifrato, ácido clofíbrico, etofibrato, fenofibrato, gemfibrozil, nicofibrato, pirifibrato, ronififibrato, simfibrato y teofibrato.

En la descripción anterior, un promotor de catabolismo de LDL es un medicamento para aumentar los receptores de LDL (lipoproteína de baja densidad), por lo tanto reduciendo el nivel de colesterol en sangre y los ejemplos incluyen los compuestos descritos en la solicitud de la patente japonesa de Kodai Hei 7-316144 o las sales de los mismos, más específicamente, N-[2-[4-bis(4-fluorofenil)metil-1-piperazinil]etil]-7,7-difenil-2,4,6- heptatrienoicoamida.

Los compuestos a base de estatina descritos anteriormente, los inhibidores de la síntesis de escualeno, los compuestos a base de fibratos y los

promotores del catabolismo de LDL se pueden reemplazar con otro compuesto químico eficaz para reducir el nivel de colesterol o triglicéridos en sangre. Los ejemplos de dicho medicamento incluyen preparaciones de derivados de ácido nicotínico tal como nicomol y niceritrol; antioxidantes tales como probucol; y preparaciones de resinas de intercambio iónico tales como coletiramina.

En la descripción anterior, un inhibidor de la enzima conversora de la angiotensina es un medicamento para inhibir la enzima conversora de la angiotensina, por lo tanto reduciendo la tensión sanguínea y al mismo tiempo, reduciendo parcialmente el nivel de azúcar en sangre de un paciente que padece diabetes. Los ejemplos incluyen captopril, enalapril, alacepril, delapril, ramipril, lisinopril, imidapril, benazepril, ceronapril, cilazapril, enalaprilat, fosfinipril, meveltipril, perindopril, quinapril, espirapril, temocapril y trandolapril.

Para la preparación de líquidos orales, los vehículos adecuados incluyen emulsiones, soluciones, suspensiones, jarabes, y similares, conteniendo opcionalmente aditivos tales como agentes humectantes, agentes emulsionantes y de suspensión, agentes edulcorantes, aromatizantes y perfumes, y similares.

Para la preparación de fluidos para administración parenteral, los vehículos adecuados incluyen soluciones, suspensiones o emulsiones acuosas o no acuosas estériles. Los ejemplos de disolventes o vehículos no acuosos son propilenglicol, polietilenglicol, aceites vegetales, tales como aceite de oliva y aceite de maíz, gelatina, y ésteres orgánicos inyectables tales como oleato de etilo. Dichas formas de dosificación también pueden contener adyuvantes tales como agentes conservantes, humectantes, emulsionantes, y dispersantes. Se pueden esterilizar, por ejemplo, mediante filtración a través de un filtro que

retiene bacterias, mediante la incorporación de agentes esterilizantes en las composiciones, mediante la irradiación de la composiciones, o mediante el calentamiento de las composiciones. También se pueden fabricar en forma de agua estéril, o algún otro medio inyectable estéril inmediatamente antes de uso.

Definiciones

Para los propósitos de la presente invención, como se describe y se reivindica en esta memoria descriptiva, los siguientes términos se definen como sigue:

El término "halo", como se usa en esta memoria descriptiva, salvo que se indique otra cosa, significa fluoro, cloro, bromo o yodo. Los grupos halo preferidos son fluoro, cloro y bromo.

El término "alquilo", como se usa en esta memoria descriptiva, salvo que se indique otra cosa, incluye los radicales de hidrocarburos monovalentes saturados que tienen restos ramificados lineales o ramificados.

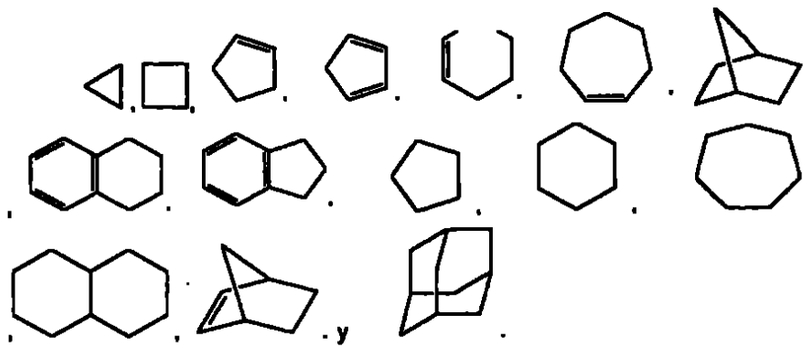
El término "alquenilo", como se usa en esta memoria descriptiva, salvo que se indique otra cosa, incluye los restos alquilo que tienen al menos un doble enlace carbono – carbono en el que alquilo es como se ha definido anteriormente e incluye los isómeros E y Z de dicho resto alquenilo.

El término "alquinilo", como se usa en esta memoria descriptiva, salvo que se indique otra cosa, incluye los restos alquilo que tienen al menos un triple enlace carbono – carbono en el que alquilo es como se ha definido anteriormente.

El término "alcoxi", como se usa en esta memoria descriptiva, salvo que se indique otra cosa, incluye grupos O-alquilo en los que alquilo es como se ha definido anteriormente.

El término "Me" significa metilo, "Et" significa etilo, y "Ac" significa acetilo.

El término "cicloalquilo", como se usa en esta memoria descriptiva, salvo que se indique otra cosa se refiere a un hidrocarburo no aromático, saturado o parcialmente saturado, monicíclico o condensado, espiro o no condensado bicíclico o tricíclico mencionado en esta memoria descriptiva que contiene un total de entre 3 y 10 átomos de carbono, preferiblemente 5 – 8 átomos de carbono en el anillo. Los cicloalquilo ejemplares incluyen los anillos monocíclicos que tienen entre 3 y 7, preferiblemente 3 – 6, átomos de carbono, tales como ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo y similares. Los ejemplos ilustrativos de cicloalquilo se derivan de, pro no se limitan a, los siguientes:

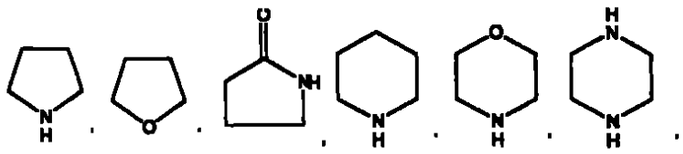


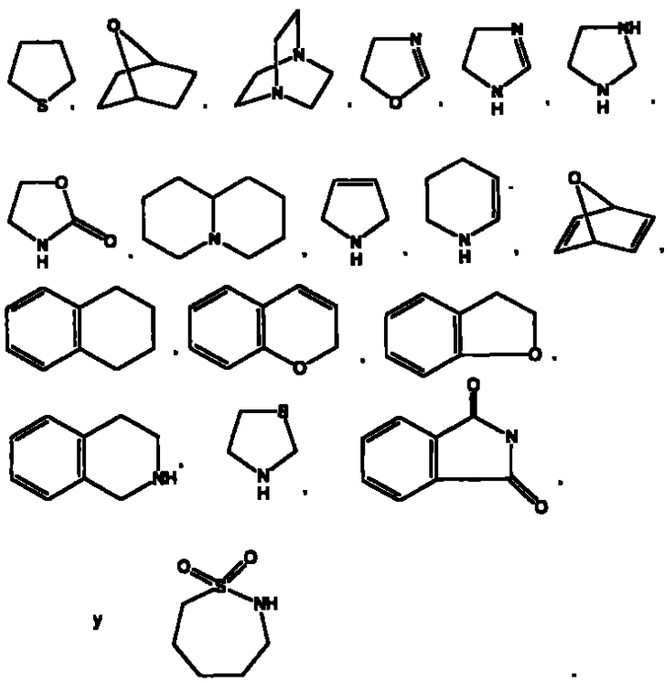
El término"arilo" como se usa en esta memoria descriptiva, salvo que se indique lo contrario, incluye un radical orgánico derivado de un hidrocarburo aromático mediante la eliminación de un hidrógeno tal como, tal como fenilo o naftilo.

La expresión "heterocíclico de 4 – 10 eslabones", como se usa en esta memoria descriptiva, salvo que se indique otra cosa, incluye los grupos heterocíclicos aromáticos y no aromáticos conteniendo entre uno y cuatro heteroátomos cada uno seleccionado entre O, S y N, en el que cada grupo

heterocíclico tiene entre 4 y 10 átomos en su sistema de anillo, y con la condición de que el anillo de dicho grupo no contenga dos átomos O o S adyacentes. Los grupos heterocíclicos no aromáticos incluyen los grupos que tienen solamente 4 átomos en su sistema de anillo, pero los grupos heterocíclicos aromáticos deben tener al menos 5 átomos en su sistema de anillo. Los grupos heterocíclicos incluyen los sistemas de anillo benzocondensados. Un ejemplo de un grupo heterocíclico de 4 eslabones es azetidinilo (derivado de azetidina). Un ejemplo de un grupo heterocíclico de 5 eslabones es tiazolilo y un ejemplo de un grupo heterocíclico de 10 eslabones es quinolinilo. Los ejemplos de los grupos heterocíclicos no aromáticos son pirrolidinilo, tetrahidrofuranilo, dihidrofuranilo, tetrahidrotienilo, tetrahidropiranilo, dihidropiranilo, tetrahidrotiopiranilo, piperidino, morfolino, tiomorfolino, tioxanilo, piperazinilo, azetidinilo, oxetanilo, tietanilo, homopiperidinilo, oxepanilo, tiepanilo, oxazepinilo, diazepinilo, tiazepinilo, 1,2,3,6-tetrahidropiridinilo, 2-pirrolinilo, 3-pirrolinilo, indolinilo, 2H-piranilo, 4H-piranilo, dioxanilo, 1,3-dioxolanilo, pirazolinilo, ditianilo, ditiolanilo, dihidropiranilo, dihidrotienilo, dihidrofuranilo, pirazolidinilo, imidazolinilo, imidazolidinilo, 3-azabiciclo[3.1.0]hexanilo, 3-azabiciclo[4.1.0]heptanilo, 3H-indol y quinolizinilo. Los ejemplos de los grupos heterocíclicos aromáticos son piridinilo, imidazolilo, pirimidinilo, pirazolilo, triazolilo, pirazinilo, tetrazolilo, furilo, tienilo, isoxazolilo, tiazolilo, oxazolilo, oxazolilo, isotiazolilo, pirrolilo, quinolinilo, isoquinolinilo, indolilo, benzimidazolilo, benzofuranilo, cinolinilo, indazolilo, indolizinilo, ftalazinilo, piridazinilo, triazinilo, isoindolilo, pteridinilo, purinilo, oxadiazolilo, tiadiazolilo, furazanilo, benzofurazanilo, benzotiofenilo, benzotiazolilo, benzoxazolilo, quinazolinilo, quinoxalinilo, naftriridinilo, y furopiridinilo. Los

grupos anteriores, ya que se derivan de los grupos enumerados anteriormente, se pueden unir en C o unir en N cuando sea posible. Por ejemplo, un grupo derivado de pirrol puede ser pirrol-1-ilo (unido en N) o pirrol-3-ilo (unido en C). Además, un grupo derivado de imidazol puede ser imidazol-1-ilo (unido en N) o imidazol-3-ilo (unido en C). Los heterocíclicos de 4 – 10 eslabones se pueden opcionalmente sustituir sobre cualquier átomo (s) de carbono, azufre o nitrógeno en el anillo por uno a dos oxo, por anillo. Un ejemplo de un grupo heterocíclico en el que 2 átomos de carbono en el anillo se sustituyen con dos restos oxo es 1,1-dioxotiomorfolinilo. Otros ejemplos ilustrativos heterocíclicos de 4 – 10 eslabones se derivan pero no se limitan a, los siguientes:

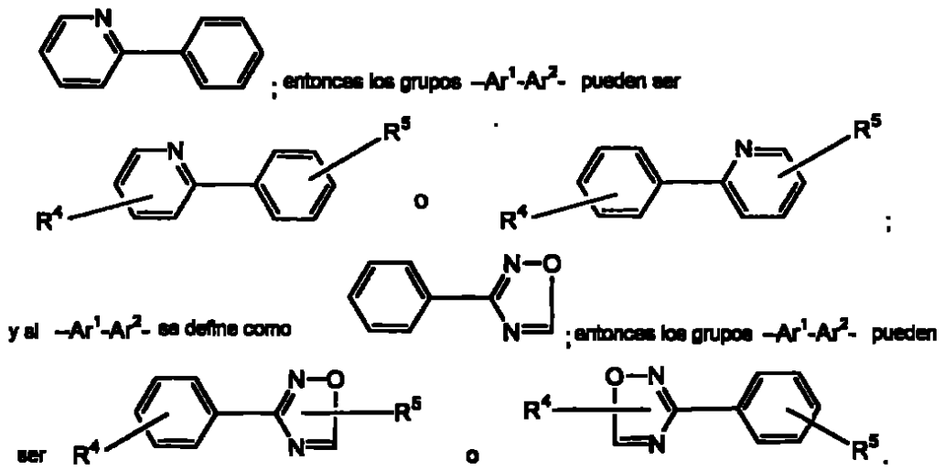




y

Salvo que se indique otra cosa, el término "oxo" se refiere a =O.

El término"-Ar^1-Ar^2-" como se usa en esta memoria descriptiva, salvo que se indique otra cosa, incluye dos anillos sin ninguna limitación del orden de acoplamientos a R^4 y R^5. Por ejemplo, -Ar^1-Ar^2- se define como



La frase "sal (es) farmacéuticamente aceptable (s)", como se usa en esta memoria descriptiva, salvo que se indique otra cosa, incluye las sales de grupos ácidos o básicos que pueden estar presentes en los compuestos de fórmula (I). Los compuestos de fórmula (I) que son básicos por naturaleza son capaces de formar una amplia diversidad de sales con diversos ácidos orgánicos o inorgánicos. Los ácidos que se pueden usar para preparar las sales de adición de ácido farmacéuticamente aceptables de dichos compuestos básicos de fórmula (I) son los que forman sales de adición de ácido no tóxicos, es decir, las sales conteniendo aniones farmacológicamente aceptables, tales como las sales acetato, bencenosulfonato, benzoato, bicarbonato, bisulfato, bitartrato, borato, bromuro, edetato de calcio, camsilato, carbonato, cloruro, clavulanato, citrato, diclorhidrato, edetato, edisilato, estolato, esilato, etilsuccinato, fumarato, gluceptato, gluconato, glutamato, glicolilarsanilato, hexilrresorcinato, hidrabamina, bromhidrato, clorhidrato, yoduro, isotionato, lactato, lactobionato, laurato, malato, maleato, mandelato, mesilato, metilsulfato, mucato, napsilato, nitrato, oleato, oxalato, pamoato, (embonato),

palmitato, pantotenato, fosfato/difosfato, poligalacturonato, salicilato, estearato, subacetato, succinato, tanato, tartrato, teoclato, tosilato, trietiododo, y valerato.

En los compuestos de fórmula (I), en los que se usan los términos como $(CR^{11}R^{12})_q$ o $(CR^{11}R^{12})_t$, R^{11} y R^{12} pueden variar con cada repetición de q o t superior a 1. Por ejemplo, cuando q o t es 2 el término $(CR^{11}R^{12})_q$ o $(CR^{11}R^{12})_t$ puede ser igual a $-CH_2-CH_2-$, $-CH(CH)_3C(CH_2CH_3)(CH_2CH_2CH_3)-$, o cualquier número de restos similares que caen dentro del alcance de las definiciones de R^{11} y R^{12}. Además, como se ha indicado anteriormente, cualquier sustituyente que comprende un grupo CH_3 (metilo), CH_2 (metileno), o CH (metino) que no se une a un grupo halógeno, SO o SO_2 o a un átomo de N, O o S soporta opcionalmente sobre dicho grupo un sustituyente seleccionado entre hidroxi, alcoxi ($C_1 - C_4$) y aminas.

El término "tratar", como se usa en esta memoria descriptiva, salvo que se indique otra cosa, significa, invertir, aliviar, inhibir el progreso de, o prevenir el trastorno o afección a la que tal término se aplica, o uno o más síntomas de tal trastorno o afección. El término "tratamiento", como se usa en esta memoria descriptiva, salvo que se indique otra cosa, se refiere al acto de tratar como se ha definido "tratar" inmediatamente antes.

El término "modular" o "modulando", como se usa en esta memoria descriptiva, se refiere a la capacidad de un modulador para un miembro de la superfamilia esteroides/tiroides de unirse bien directa (mediante unión al receptor como ligando) o indirectamente (como precursor de un ligando o un inductor que promueve la producción de ligando a partir de un precursor) inducen la expresión del (de los) gen (s) mantenido (s) bajo control de expresión hormonal, o para reprimir la expresión del (de los) gen (s) mantenido

(s) bajo dicho control.

El término "obesidad" u "obeso", como se usa en esta memoria descriptiva, se refiere generalmente a individuos que están al menos aproximadamente 20 – 30% por encima del peso medio para su edad, sexo y altura. Técnicamente, "obeso" se define, para hombres, como los individuos cuyo índice de masa corporal es mayor que 27,8 kg/m^2, y para mujeres, como los individuos cuyo índice de masa corporal es mayor que 27,3 kg/m^2. Los expertos en la técnica reconocerán fácilmente que el procedimiento de la invención no se limita a los que caen dentro del criterio anterior. De hecho, el procedimiento de la invención puede también ponerse en práctica ventajosamente en individuos que caen fuera de estos criterios tradicionales, por ejemplo, por los que son propensos a obesidad.

El término "trastornos inflamatorios", como se usa en esta memoria descriptiva, se refiere a los trastornos tales como artritis reumatoide, espondilitis anquilosante, artritis psoriática, psoriasis, condrocalcinosis, gota, enfermedad inflamatoria del intestino, colitis ulcerosa, enfermedad de Crohn, fibromialgia y caquexia.

La frase "cantidad terapéuticamente eficaz", como se usa en esta memoria descriptiva, se refiere a la cantidad de fármaco o agente farmacéutico que provocará la respuesta médica o biológica de un tejido, sistema, animal o ser humano que busca un investigador, veterinario, doctor u otro.

La frase "cantidad ... eficaz para reducir los niveles de glucosa en sangre", como se usa en esta memoria descriptiva, se refiere a los niveles de compuesto suficientes para proporcionar concentraciones circulantes lo suficientemente altas para lograr el efecto deseado. Dicha concentración

típicamente cae en el intervalo de aproximadamente 10 nM a 2 µM; siendo preferidas las concentraciones en el intervalo entre aproximadamente 100 nM hasta 500 nM. Como se ha indicado anteriormente, ya que la actividad de los diferentes compuestos que caen dentro de la definición de fórmula (I) como se ha expuesto anteriormente puede variar considerablemente, y ya que los sujetos individuales pueden presentar una amplia variación en la gravedad de los síntomas, es el médico el que determina una respuesta del sujeto al tratamiento y de acuerdo con lo anterior puede variar las dosificaciones.

La frase "resistencia a la insulina", como se usa en esta memoria descriptiva, se refiere a la reducción de la sensibilidad a las acciones de la insulina en el cuerpo entero o en tejidos individuales, tales como el tejido muscular esquelético, tejido miocárdico, tejido graso o tejido hepático. La resistencia a la insulina se produce en muchos individuos con o sin diabetes mellitus.

La frase "síndrome de resistencia a la insulina", como se usa en esta memoria descriptiva, se refiere al conjunto de manifestaciones que incluyen resistencia a la insulina, hiperinsulinemia, diabetes mellitus no insulinodependiente (abreviadamente en inglés NIDDM), hipertensión arterial, obesidad central (visceral), y dispilidemia.

La frase "en combinación con", como se usa en esta memoria descriptiva, significa que el compuesto de los ácidos carboxílicos alfa sustituidos de fórmula (I) se puede administrar inmediatamente antes, inmediatamente después, simultáneamente, o cualquier combinación de antes, después, o simultáneamente, con estos otros agentes descritos en los párrafos anteriores. Así que, el compuesto de los ácidos carboxílicos alfa sustituidos de

fórmula (I) y los otros agentes se pueden administrar simultáneamente bien como una composición única o como dos composiciones separadas o secuencialmente como dos composiciones separadas.

Ciertos compuestos de fórmula (I) pueden tener centros asimétricos y por lo tanto existir en diferentes formas enantioméricas. Todos los isómeros y estereoisómeros ópticos de los compuestos de fórmula (I), y las mezclas de los mismos, se considera que están dentro del alcance de la invención. Con relación a los compuestos de fórmula (I), la invención incluye el uso de un racemato, una o más formas enantioméricas una o más formas diastereoméricas, o mezclas de las mismas. Los compuestos de fórmula (I) pueden también existir como tautómeros. La invención se refiere al uso de todos estos tautómeros y mezclas de los mismos.

Ciertos grupos funcionales contenidos en los compuestos de la presente invención se pueden sustituir con grupos bioisostéricos, es decir, los grupos que tienen requerimientos espaciales o electrónicos similares al grupo precursor, pero exhibiendo propiedades fisicoquímicas u otras, diferentes o mejoradas. Los ejemplos adecuados los conocen bien los expertos en la técnica, e incluyen, pero no se limitan a los restos descritos en Patini y col., *Chem. Rev,* 1996, 96, 3147 – 3176 y las referencias citadas en ese documento.

La invención sujeto también incluye compuestos marcados con isótopos, que son idénticos a los relatados en la fórmula (I), pero por el hecho de que uno o más átomos se sustituyen por un átomo que tiene una masa atómica o número másico diferente de la masa atómica o número másico habitualmente encontrado en la naturaleza. Los ejemplos de isótopos que se pueden incorporar en los compuestos de la invención incluyen los isótopos de

hidrógeno, carbono, nitrógeno, oxígeno, fósforo, flúor, y cloro, tales como ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, y ^{36}Cl, respectivamente. Los compuestos de la presente invención, profármacos de los mismos, y las sales farmacéuticamente aceptable de dichos compuestos que contienen los isótopos anteriormente mencionados y/u otros isótopos de otros átomos están dentro del alcance de esta invención. Ciertos compuestos marcados con isótopos de la presente invención, por ejemplo en los que se incorporan los isótopos radiactivos tales como ^{3}H y ^{14}C, son útiles en ensayos de distribución en tejidos de fármacos y/o sustratos. Los isótopos tritiados, es decir, ^{3}H y de carbono 14, es decir ^{14}C, se prefieren particularmente por su fácil preparación y detectabilidad. Además, la sustitución con isótopos más pesados tales como deuterio, es decir, ^{2}H, puede producir ciertas ventajas terapéuticas que se producen por una estabilidad metabólica mayor, por ejemplo, incremento de la semivida *in vivo* o reducción de los requerimientos de dosificación, por lo tanto, se puede preferir en algunas circunstancias. Los compuestos marcados con isótopos de fórmula (I) de esta invención y profármacos de los mismos se pueden preparar generalmente llevando a cabo los procedimientos descritos en esta memoria descriptiva en los esquemas y/o los ejemplos y las preparaciones más adelante, mediante la sustitución de un reactivo no marcado con isótopos por un reactivo disponible marcado con isótopos.

Esta invención también comprende las composiciones farmacéuticas que los contienen y los procedimientos de tratamiento de infecciones bacterianas mediante la administración de los compuestos de fórmula 1. Los compuestos de fórmula 1 que tienen grupos amino, amido, hidroxi o caboxílico libres se pueden convertir en profármacos. Los profármacos incluyen los

compuestos en los que un resto aminoácido, o una cadena de polipéptidos de dos o más residuos (por ejemplo dos, tres o cuatro) aminoácidos está covalentemente unida a través de un enlace amida o éster a un grupo amino, hidroxi o carboxílico libre de compuestos de fórmula 1. Los restos aminoácido incluyen pero no se limitan a los 20 aminoácidos de origen natural comúnmente designados por tres símbolos de letras y también incluyen 4-hidroxiprolina, hidroxilisina, demosina, isodemosina, 3-metilhistidina, norvalina, beta alanina, ácido gammabutírico, citrulina, homocisteína, homoserina, ornitina y metioninasulfona. Los tipos adicionales de profármacos también están comprendidos. Por ejemplo, los grupos carboxílicos libres se pueden derivatizar como amidas o ésteres de alquilo. Los grupos hidroxi libres se pueden derivatizar usando los grupos que incluyen pero no se limitan a hemisuccinatos, ésteres fosfato, dimetilaminoacetatos, y fosforiloximetoxiloxicarbonilos, como se indica en *Advanced Drug Delivery Reviews*, 1996, 19, 115. También se incluyen los profármacos de carbamato de grupos hidroxi y amino, como son los profármacos de carbonato, ésteres sulfonato, y ésteres sulfato de los grupos hidroxi. La derivatización de los grupos hidroxi como éteres de (aciloxi)metilo y (aciloxi)etilo en los que el grupo acilo puede ser un éster alquílico, opcionalmente sustituidos con grupos que incluyen pero no se limitan a las funcionalidades de éter, amina y ácido carboxílico, o cuando el grupo acilo es un éster de aminoácido como se ha descrito anteriormente, también están comprendidas. Los profármacos de este tipo se describen en *J. Med. Chem.*, 1996, 39, 10. Las aminas libres también se pueden derivatizar como amidas, sulfonamidas o fosfonamidas. Todos estos restos de profármacos pueden incorporar pueden incorporar los grupos que iricluyen pero no se limitan a las

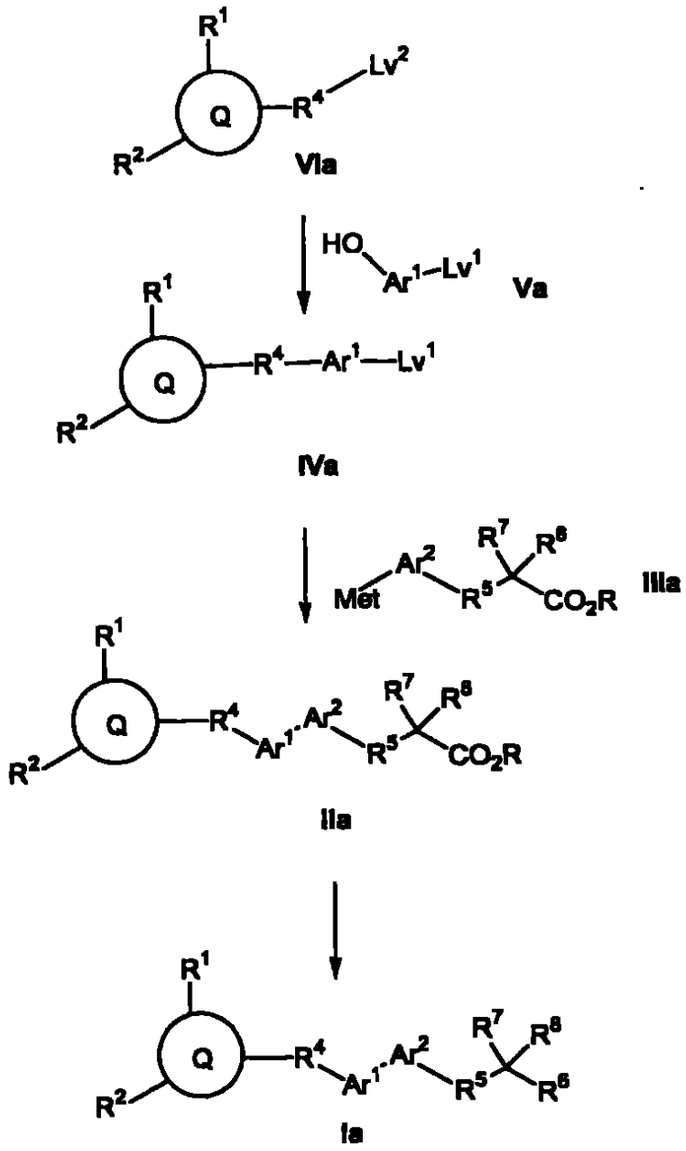
funcionalidades de éter, amina y ácido carboxílico.

Otros aspectos, ventajas, y características preferidas de la invención se harán evidentes a partir de la descripción detallada más adelante.

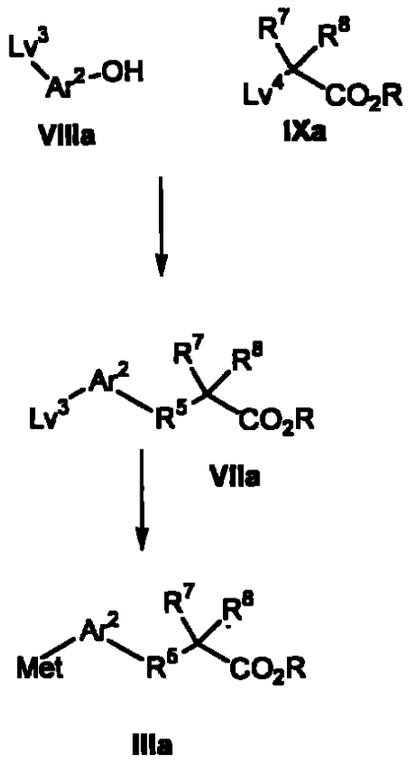
Descripción detallada y realizaciones preferidas de la invención

El siguiente esquema de reacción ilustra la preparación de los compuestos de la presente invención. Salvo que se indique otra cosa, R – R^{17}, Q, Y, Ar^1 – Ar^4, y anillo A, en el esquema de reacción y descripción que sigue son como se han definido anteriormente.

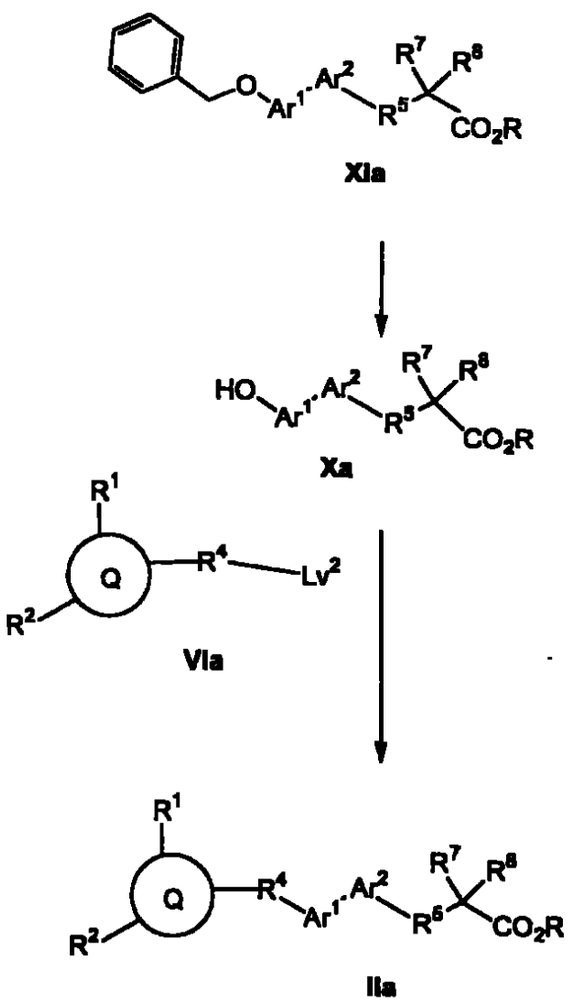
Esquema 1


R1
Lv2
Q
R4
R2
VIa
HO
Ar1–Lv1
Va
R1
Q
R4—Ar1—Lv1
R2
IVa
R7
R8
Ar2
Met
R5
CO2R
IIIa
R1
Q
R4
Ar1
Ar2
R7
R8
R5
CO2R
R2
IIa
R1
Q
R4
Ar1
Ar2
R7
R8
R5
R6
R2
Ia

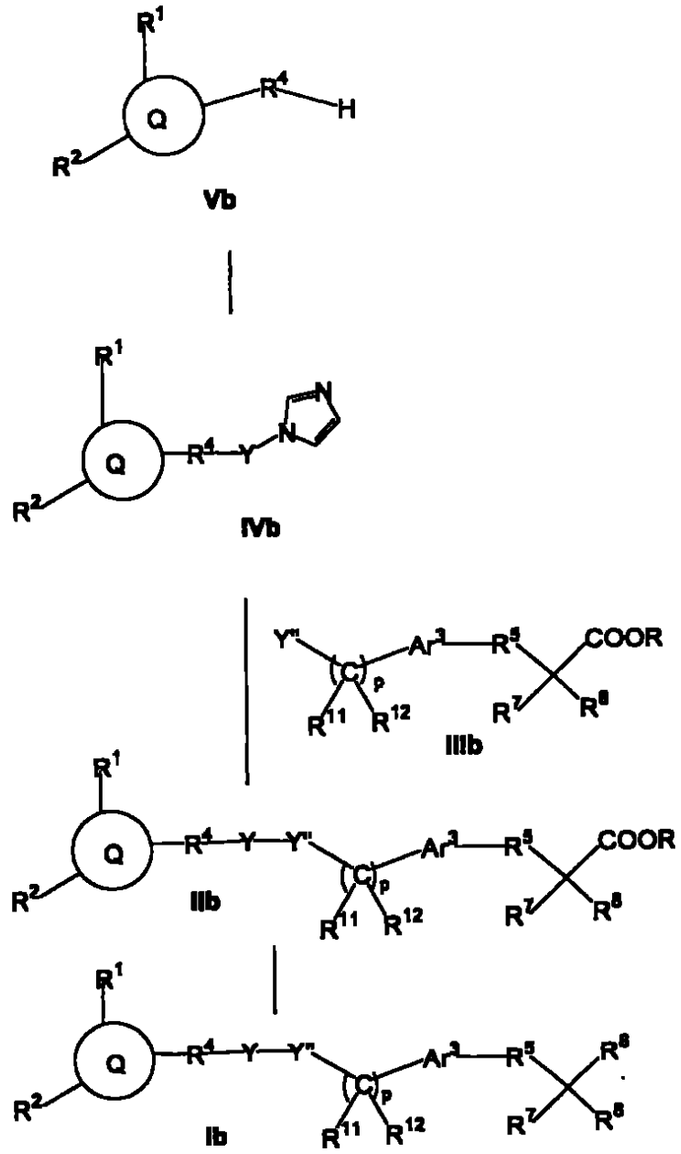
Esquema 2


Lv3
Ar2-OH
VIIIa
R7
R8
Lv4
CO2R
IXa
Lv3
Ar2
R5
R7
R8
CO2R
VIIa
Met
Ar2
R5
R7
R8
CO2R
IIIa

Esquema 3



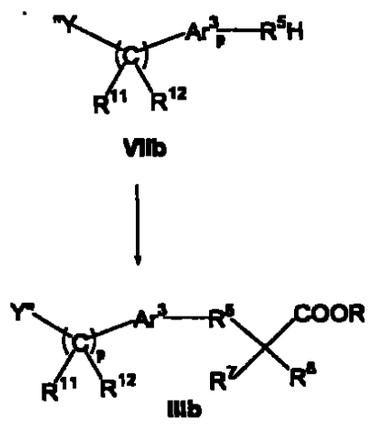
Esquema 4



R^5 es $-(CR^{11}R^{12})_m-Z-(CR^{11}R^{12})_s$; en el que Z es –O–, $-NR^{10a}-$, $-S(O)_j-$; en el que cada m y s son independientemente 0, 1, 2 ó 3; y en el que j

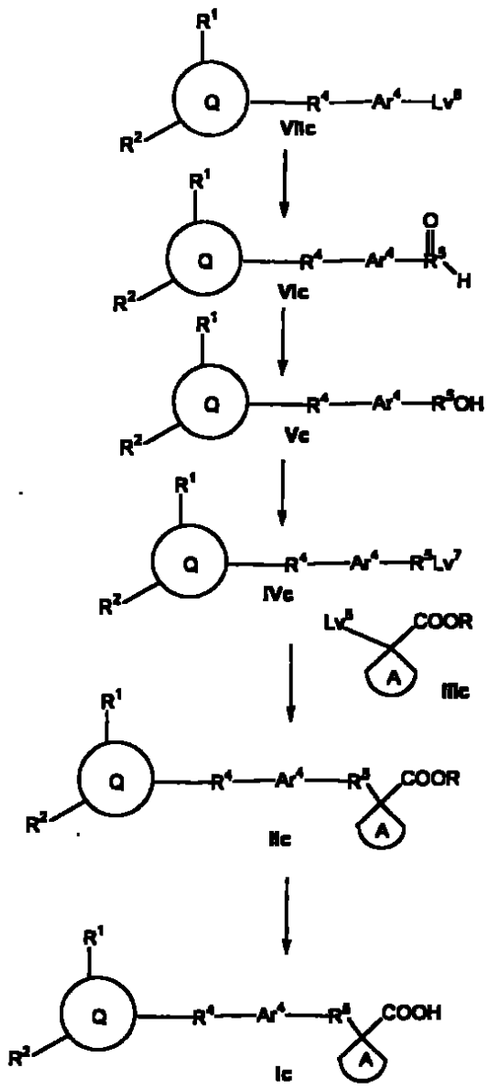
es 0, 1, ó 2

Esquema 5



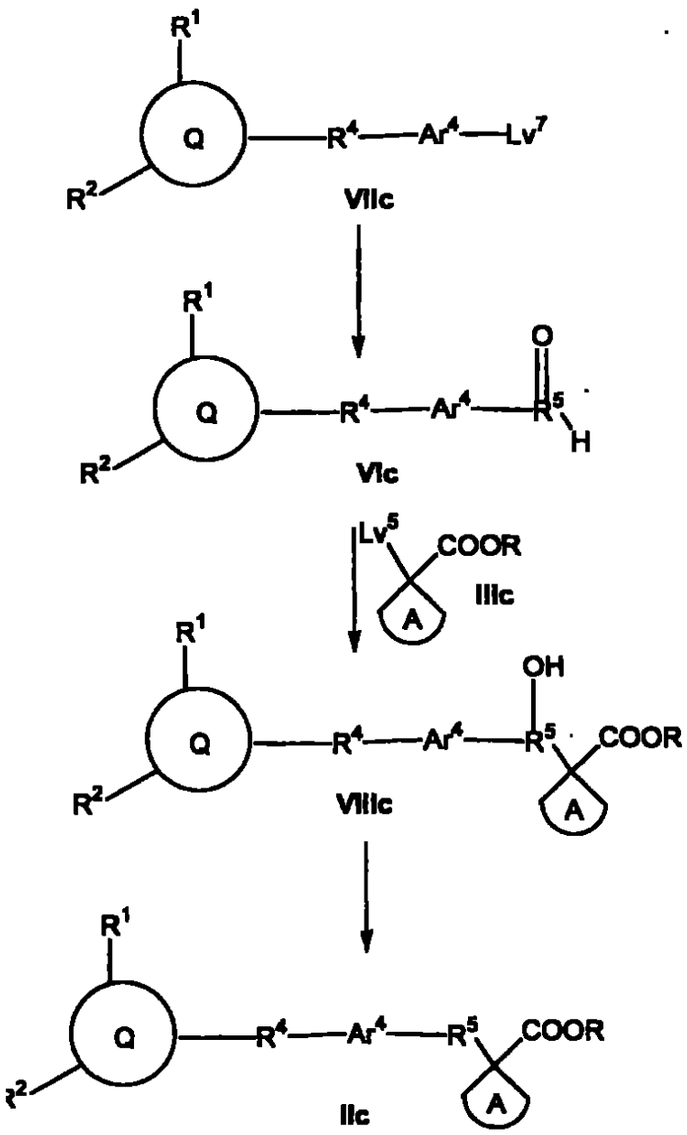
R^5 es $-(CR^{11}R^{12})_m-Z-(CR^{11}R^{12})_s$; en el que Z es –O–, $-NR^{10a}$-, $-S(O)_j$-; en el que cada m y s son independientemente 0, 1, 2 ó 3; y en el que j es 0, 1, ó 2

Esquema 6



R^5 es $-(CR^{11}R^{12})_m-Z-(CR^{11}R^{12})_s$; en el que Z es $-CH_2-$; en el que cada m y s son independientemente 0, 1, 2 ó 3;

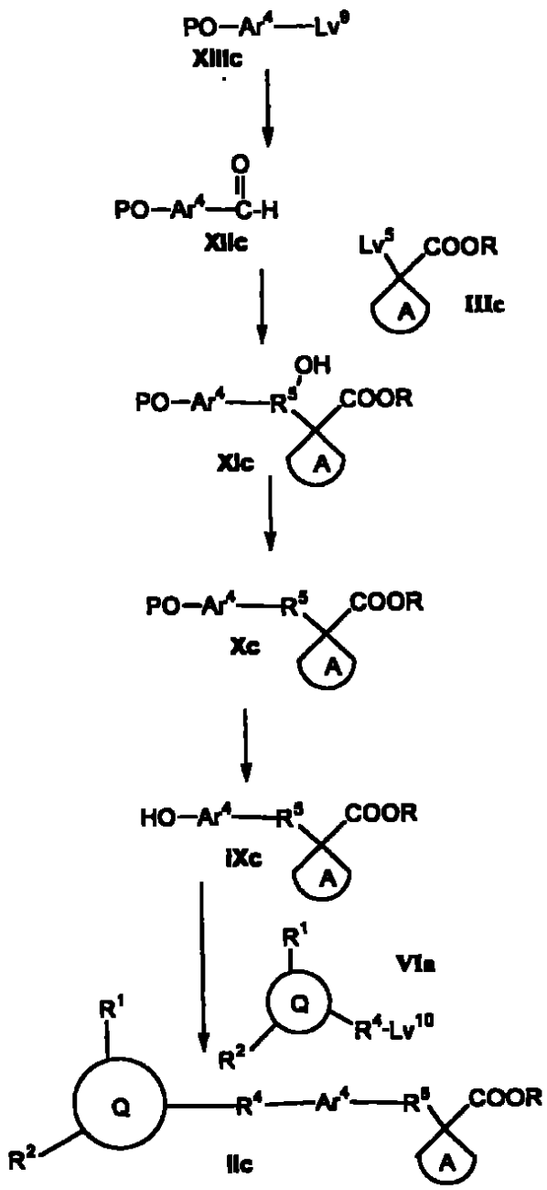
Esquema 7



R^5 es $-(CR^{11}R^{12})_m-Z-(CR^{11}R^{12})_s$; en el que Z es $-CH_2-$; en el que cada

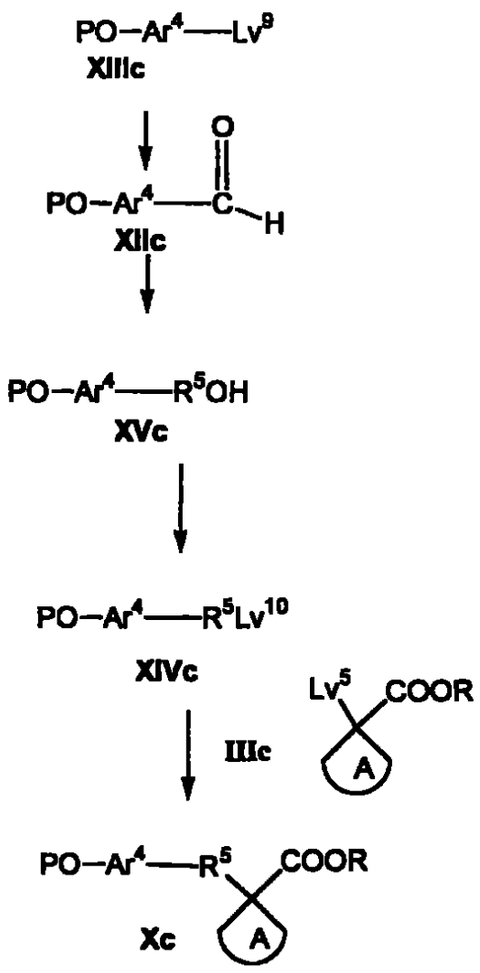
m y s son independientemente 0, 1, 2 ó 3;

Esquema 8



R^5 es $-(CR^{11}R^{12})_m-Z-(CR^{11}R^{12})_s-$; en el que Z es $-CH_2-$; en el que cada m y s son independientemente 0, 1, 2 ó 3;

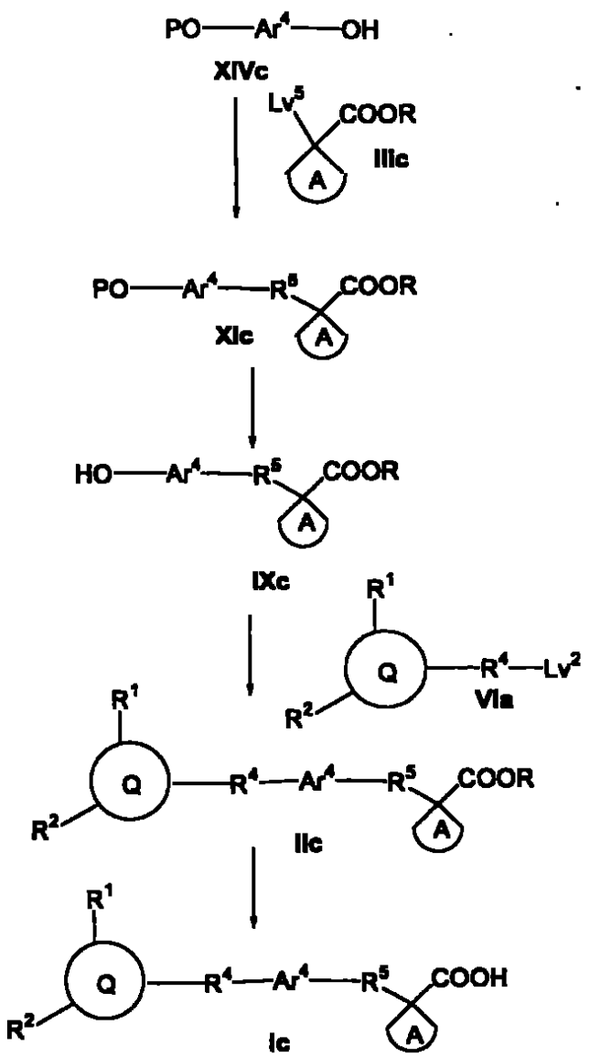
Esquema 9



R^5 es $-(CR^{11}R^{12})_m-Z-(CR^{11}R^{12})_s$; en el que Z es $-CH_2-$; en el que cada m y s son independientemente 0, 1, 2 ó 3;

54
135

Esquema 10

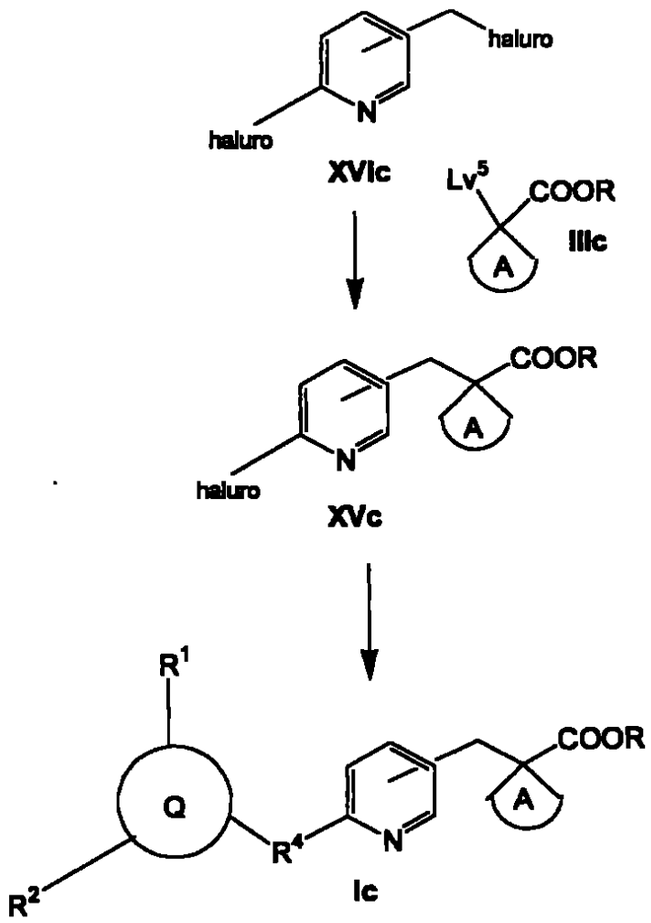


R^5 es $-(CR^{11}R^{12})_m-Z-(CR^{11}R^{12})_s$; en el que Z es –O–, $-NR^{10a}-$, $-S(O)_j-$; en el que cada m y s son independientemente 0, 1, 2 ó 3; y en el que j es 0, 1, ó 2

5

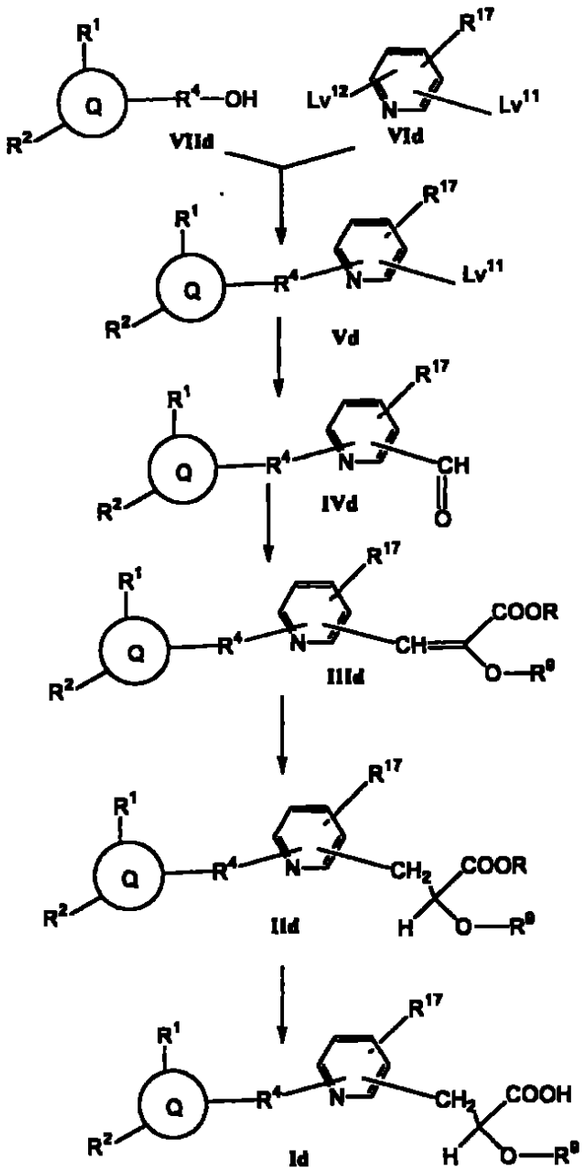
155
156

Esquema 11

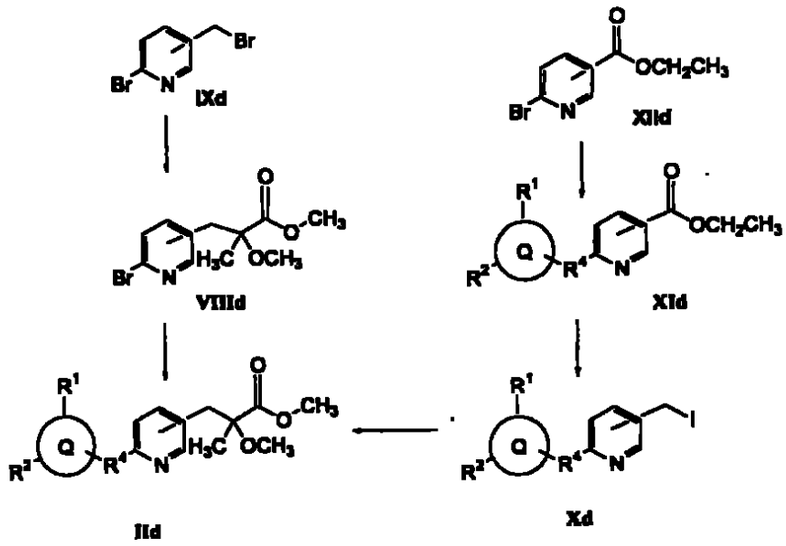


156
157

Esquema 12



Esquema 13



Con referencia al esquema 1 anterior, el compuesto de fórmula Ia se puede preparar mediante hidrólisis de los compuestos IIa, en los que el grupo CO_2R es un grupo éster hidrolizable tal como éster metílico (CO_2-CH_3) o éster etílico (CO_2-CH_2CH_3), mediante hidróxidos de metales alcalinos (por ejemplo, NaOH, LiOH, KOH) en un disolvente adecuado (por ejemplo, THF, metanol acuoso o combinaciones de los mismos) a una temperatura entre 0 y 10 grados centígrados o calentando en un sintetizador de microondas. Los compuestos de fórmula IIa se pueden preparar mediante una reacción de acoplamiento del compuesto IVa, en el que Lv^1 es Cl, Br, I, o triflato, y un compuesto organometálico IIIa, en el que Met = ácido bórico o éster, estannano, etc., y el grupo CO_2R es como se ha descrito anteriormente, mediado por un catalizador

de paladio (0) u otro metal de transición. El compuesto **IVa** se puede obtener mediante alquilación del compuesto **Va**, en el que Lv^1 es como se ha descrito anteriormente, con los compuestos **VIa**, en el que Lv^2 es Cl, Br, I, o triflato.

Con relación al esquema 2 anterior, el compuesto de fórmula **IIIa**, que se usa en el esquema 1, se puede obtener a partir de los compuestos **VIIa**, en el que Lv^3 es Cl, Br, I, o triflato, mediante reacciones de acoplamiento mediadas por paladio (0) con un reactivo tal como pinacolatodiborano. Los compuestos **VIIa**, en los que Lv^3 es como se ha descrito anteriormente, se puede obtener mediante alquilación de los compuestos **VIIIa**, en los que Lv^3 es como se ha descrito anteriormente, con el compuesto **IXa**, en el que Lv^4 es Cl, Br, I, o triflato.

Con relación al esquema 3 anterior, los ésteres **IIa**, que se usan en el esquema 1, en los que el grupo CO_2R es como se ha descrito anteriormente, también se pueden preparar mediante alquilación de un compuesto **Xa**, en el que el grupo CO_2R es como se ha descrito anteriormente, con el compuesto **VIa**, en el que Lv^2 es como se ha descrito anteriormente en la descripción del esquema 1. Los compuestos **Xa** se pueden obtener a partir del compuesto **XIa**, en el que el grupo CO_2R es como se ha descrito anteriormente, mediante la reacción del compuesto **XIa** con un agentes desprotector, tal como con hidrógeno gas sobre un catalizador metálico (por ejemplo, paladio sobre carbono) en un disolvente adecuado (por ejemplo, THF, metanol, etanol) a una temperatura entre 0 grados Celsius y 100 grados Celsius.

Los compuestos **XIa** están comercialmente disponibles o los pueden preparar los expertos en la técnica.

Con relación al esquema 4 anterior, los compuestos de fórmula **Ib**; en los

que R^5 es $-(CR^{11}R^{12})_m-Z-(CR^{11}R^{12})_s$; en el que Z es –O–, $-NH^{10a}$, o $-S(O)_j$; en el que cada m y s son independientemente 0, 1, 2, ,o 3; y en el que cada m y s son independientemente 0, 1, 2, ó 3; y en el que j es 0, 1, ó 2; se puede preparar mediante hidrólisis de los compuestos **IIb**, en el que R^5 es como se ha descrito en los compuestos de fórmula **Ib** y el grupo CO_2R es como se ha descrito anteriormente, mediante un hidróxido de metal alcalino (por ejemplo, NaOH, LiOH, KOH) en un disolvente adecuado (por ejemplo, THF acuoso, metanol acuoso o combinaciones de los mismos) a una temperatura de 0 grados Celsius y 100 grados Celsius. Los compuestos de fórmula **IIb**, en la que R^5 es como se ha descrito en los compuestos de fórmula **Ib**, se pueden preparar mediante la reacción de los compuestos de fórmula **IIIb**, en los que R^5 es como se ha descrito en los compuestos de fórmula **IIb** y el grupo CO_2R es como se ha descrito anteriormente, con un agente acilante activado tal como **VIb** en un disolvente adecuado (por ejemplo, THF, acetonitrilo, dioxano, tolueno) a una temperatura entre 0 grados Celsius y 100 grados Celsius. Los compuestos **IVb** se pueden obtener a partir del compuesto **Vb** mediante la reacción del compuesto **Vb** con el compuesto **VIb**, en los que Lv^6 es un grupo saliente. El compuesto adecuado **VIb** adecuado incluye N,N'-carbonildiimidazol.

Los compuestos **Vb** y **VIb** están comercialmente disponibles o los pueden preparar los expertos en la técnica.

Con relación al esquema 5 anterior, los compuestos de fórmula **IIIb**, que se usan en el esquema 4, en los que R^5 es como se ha descrito en la descripción del esquema 4 y el grupo CO_2R es como se ha descrito anteriormente, se pueden preparar mediante la reacción de un compuesto **VIIb** en el que R^5 es como se ha descrito en el párrafo anterior, con un electrófilo

adecuado de fórmula Lv^6 –$C(R^7R^8)$-COOR, en el que Lv^6 es un grupo saliente tal como halo, en presencia de una base (por ejemplo, carbonato de cesio, carbonato potásico) en un disolvente adecuado (por ejemplo, THF, DMF, acetonitrilo, o DMSO) a una temperatura entre 0 grados Celsius y 100 grados Celsius. Los electrófilos adecuados de fórmula Lv^6 –$C(R^7R^8)$-COOR incluyen 2-bromo-2-metilpropanoato de metilo. Los compuestos **VIIb** están comercialmente disponibles o los pueden preparar los expertos en la técnica.

Los compuestos de fórmula **Ib**, **IIb**, **IIIb**, y **VIIb**; en los que R^5 es –$(CR^{11}R^{12})_m$ –Z– $(CR^{11}R^{12})_s$; en el que Z es –CH_2 –, y en el que cada m y s son como se han descrito anteriormente; se pueden preparar mediante los procedimientos conocidos por los expertos en la técnica.

Con relación al esquema 6 anterior, los compuestos de fórmula **Ic**, en los que R^5 es –$(CR^{11}R^{12})_m$ –Z– $(CR^{11}R^{12})_s$; en el que Z es –CH_2 –, se pueden preparar mediante hidrólisis de los compuestos **IIc**, en los que el grupo CO_2R es como se ha descrito anteriormente, mediante un hidróxido de metal alcalino (por ejemplo, NaOH, LiOH, KOH) en un disolvente adecuado (por ejemplo, THF acuoso, metanol acuoso o combinaciones de los mismos) a una temperatura de 0º grados Celsius y 100 grados Celsius o calentando en un sintetizador de microondas. Los compuestos **IIc** se pueden preparar mediante alquilación del compuesto **IIIc**, en el que Lv^5 es un grupo saliente, con el compuesto **IVc** (cuando Lv^7 es yoduro, bromuro, cloruro u otro grupo saliente). Se pueden usar diversos procedimientos para efectuar esta reacción, tal como la desprotonación del compuesto **IIIc** (Lv^5 = H) con una base por ejemplo, bis(trimetilsilil)amida de sodio. Los compuestos **IVc** se pueden preparar a partir de los compuestos **Vc** mediante una reacción con un agente de halogenación o

sistema de halogenación, por ejemplo, cloruro de oxalilo y dimetilformamida o a partir de otro haluro (por ejemplo, reacción del compuesto IVc, Lv^7 = Cl^- con yoruro sódico). Los compuestos Vc se pueden preparar a partir de los compuestos VIc mediante la reacción de los compuestos VIIIc con un agente reductor, tal como borohidruro sódico. Los compuestos VIc se pueden obtener a partir del compuesto VIIc (Lv^8 = Br u otro halógeno) mediante intercambio metal – halógeno (por ejemplo, con butil-litio) seguido de reacción con dimetilformamida.

Como alternativa, con relación al esquema 7 anterior, los compuestos de fórmula IIc, en los que R^5 es $-(CR^{11}R^{12})_m-Z-(CR^{11}R^{12})_s$; en el que Z es $-CH_2-$, se pueden preparar mediante desoxigenación reductora del compuesto VIIIc usando un silano y una fuente de ácido, típicamente trietilsilano y ácido trifluoroacético. Los compuestos VIIIc se pueden obtener mediante la adición del compuesto IIIc al compuesto VIc. Se pueden usar diversos procedimientos para efectuar esta reacción tal como desprotonación de IIIc (Lv^5 = H) con una base por ejemplo, diisopropilamiduro de litio, o activación de tipo Reformatsky de IIIc (Lv^5 = Br) con un metal o sal metálica (por ejemplo, cloruro de cromo (II)). Los compuestos VIc se pueden obtener a partir del compuesto VIIc (Lv^8 = Br u otro halo) mediante intercambio metal – halógeno (por ejemplo con butil-litio) seguido de la reacción con dimetilformamida.

Como alternativa, con relación al esquema 8 anterior, el compuesto IIc, en el que R^5 es $-(CR^{11}R^{12})_m-Z-(CR^{11}R^{12})_s$; en el que Z es $-CH_2-$, se puede obtener mediante la reacción de los compuestos IXc con parejas de acoplamiento adecuadas de fórmula VIa. Estas reacciones se pueden efectuar usando los electrófilos VIa (por ejemplo, Lv^2 = haluros, ésteres sulfonato) en

presencia de una base (por ejemplo, carbonato de cesio) o con alcoholes (Lv^2 = OH) en condiciones de tipo Mitsunobu (por ejemplo, trifenilfosfina y dietildiazodicarboxilato). Los compuestos **IXc** se pueden preparar mediante la desprotección de los compuestos protegidos **Xc**. Los grupos protectores adecuados pueden incluir alilo, bencilo, etc. La desprotección de **Xc** (P = alilo) se puede lograr mediante la exposición a un metal de transición soluble (por ejemplo, tetraquis(trifenilfosfina)paladio (0)) en presencia de una base, por ejemplo, morfolina.

Los intermedios **Xc** – **XIIIc** se pueden preparar mediante los procedimientos descritos en el esquema 6.

Como alternativa, con relación al esquema 9 anterior, el compuesto **Xc** se puede preparar mediante la reacción del compuesto **XIVc** (por ejemplo, Lv^{10} = haluros, ésteres sulfonato) con el compuesto **IIIc**, en el que Lv^5 es como se ha descrito anteriormente. El compuesto **XIVc** se pueden preparar mediante la reacción del compuesto **XVc** con $(C = O)Cl_2$ en un disolvente aprótico polar tal como dimetilformamida. El compuesto **XVc** se puede preparar mediante la reacción del compuesto **XIIc** con un agente reductor, tal como borohidruro sódico. Los compuestos **XIIIc** se pueden preparar mediante el procedimiento desrito en el esquema 6.

Como alternativa, con relación al esquema 10 anterior, el compuesto de fórmula **Ic**, en el que R^5 es $-(CR^{11}R^{12})_m-Z-(CR^{11}R^{12})_s$; en el que Z es –O–, $-NR^{10a}-$, o $-S(O)_j-$; en el que cada m y s son independientemente 0, 1, 2, ó 3; y en el que j es 0, 1, ó 2; se puede preparar mediante la hidrólisis de los compuestos **IIc** mediante hidróxidos de metales alcalinos (por ejemplo, NaOH, LiOH, KOH) en un disolvente adecuado (por ejemplo THF acuoso, metanol

acuoso o mezclas de los mismos) a una temperatura entre 0 grados Celsius y 100 grados Celsius o calentando en un sintetizador de microondas. Los compuestos de fórmula IIc se pueden obtener mediante la reacción de los compuestos IXc con parejas de acoplamiento adecuados. Estas reacciones se pueden efectuar usando electrófilos (por ejemplo, VIa; Lv^2 = haluros, ésteres sulfonatos) en presencia de una base (por ejemplo, carbonato de cesio, carbonato potásico o *t*-butóxido potásico) o con alcoholes (VIa; Lv^2 = OH) bajo condiciones de tipo Mitsunobu (por ejemplo, trifenilfosfina y dietilazodicarboxilato). Los compuestos IXc se pueden preparar mediante la desprotección de los compuestos XIc en los que P es un grupo protector. Los grupos protectores P adecuados pueden incluir alilo, bencilo, etc. La desprotección de XIc (P = alilo) se puede lograr mediante la exposición a un metal de transición soluble (por ejemplo, tetraquis(trifenilfosfina)paladio (0)) en presencia de una base por ejemplo morfolina o mediante reducción (XIc; P = bencilo) con hidrógeno gas sobre un catalizador metálico (por ejemplo, paladio sobre carbono) en un disolvente adecuado (por ejemplo, THF, metanol, etanol) a una temperatura entre 0 grados Celsius y 100 grados Celsius. Los compuestos XIc se pueden obtener mediante alquilación de los compuestos XIVc con el compuesto IIIc (Lv^5 = Cl, Br, I, triflato, como se ha descrito anteriormente).

Con relación al esquema 11 anterior, en ciertos casos la alquilación de un anión enolato del compuesto IIIc con un bencilhaluro que tiene la fórmula XVIc produce los compuestos XVc. Los compuestos XVc se pueden convertir en los compuestos Ic mediante por ejemplo reacción de acoplamiento mediada por paladio en un disolvente conocido por los expertos en la técnica (por

ejemplo, marzo, Advanced organic Chemistry, edición cuarta).

Con relación al esquema 12 anterior, los compuestos de fórmula Id se pueden preparar mediante hidrólisis de los compuestos IId por hidróxidos de metales alcalinos (por ejemplo, NaOH, LiOH, KOH) en un disolvente adecuado (por ejemplo, THF acuoso, metanol acuoso o combinaciones de los mismos) a una temperatura entre 0 grados Celsius y 100 grados Celsius. Los compuestos de fórmula IId se pueden preparar mediante la reacción de los compuestos IIId con un agente de hidrogenación apropiado tal como hidrógeno gas en un catalizador metálico (por ejemplo, paladio o carbono) en un disolvente adecuado (por ejemplo, THF, metanol, etanol) a una temperatura entre 0 grados Celsius y 100 grados Celsius. Los compuestos de fórmula IIId se pueden preparar mediante la reacción de compuestos IVd con un reactivo de trifenilfosfina apropiado que tiene la fórmula $(C_6H_5)_3P^+$-CH(OR^9)(COOR) Cl^- en una reacción de Wittig. Los reactivos de trifenilfosfina adecuados incluyen cloruro de 1,2-dietoxi-2-oxoetil)(Trifenil)fosfonio. Los compuestos de fórmula IVd se pueden preparar mediante la reacción de los compuestos Vd como se describe en el esquema 9. Los compuestos de fórmula Vd se pueden preparar mediante la reacción de los compuestos VId y VIId como se describe en el esquema 9.

Como alternativa, los compuestos de fórmula IId se pueden preparar mediante los procedimientos del esquema 13. Con relación al esquema 13, la alquilación del anión enolato de 2-metoxipropanoato de metilo con un haluro de bencilo IXd produce los productos VIIId. Los compuestos VIIId se pueden elaborar en los compuestos IId mediante por ejemplo, una reacción de acoplamiento mediada por paladio. Los compuestos IId también se pueden

preparar a partir de los compuestos **Xd**. Los compuestos **Xd** se pueden preparar a partir de los compuestos **XIId** mediante una secuencia de reacciones tales como (i) reacción de acoplamiento mediada por paladio para formar los compuestos **XId**, y (ii) reducción del éster a alcohol, y (iii) formación de haluro para formar los compuestos **IId**.

Cualquiera de los compuestos anteriores de fórmula I y cualquiera de los compuestos en los esquemas 1 – 13 anteriores se pueden convertir en otro compuesto análogo mediante manipulaciones químicas habituales. Estas manipulaciones químicas se conocen por los expertos en la técnica e incluyen a) eliminación del grupo protector mediante procedimientos indicados en T. W. Greene y P. G. M. Wuts, "Protective Groups in Organics Synthesis", edición segunda, John Wiley and Sons, New York, 1991; b) desplazamiento de un grupo saliente (haluro, mesilato, tosilato, etc.) con una amina primaria o secundaria, tiol o alcohol para formar una amina secundaria o terciaria, tioéter o éter, respectivamente; c) tratamiento de carbamatos de fenilo (o fenilo sustituido) con aminas primarias o secundarias para formar las correspondientes ureas como en Thavonekham, B y col., Synyhesis (1997), 10, p. 1189; d) reducción de alcoholes propargílicos u homopropargílicos o aminas primarias protegidas con N-BOC a los correspondientes derivados E-alílicos o E-homoalílicos mediante tratamiento con bis(2-metoxietoxi)aluminiohidruro de sodio (Red-Al) como en Denmark, S. E.; Jones, T. K. J. Org. Chem. (1982) 47, 4595 – 4597 o van Benthem, R. A. T. M; Michels, J. J.; Speckamp, W. N. Synlett (1994), 368 – 370; e) reducción de alquinos a los derivados de Z-alqueno correspondientes mediante tratamiento con hidrógeno gas y un catalizador de Pd como en Tomassy, B. y col. Synth. Commun. (1998), 28, p.

1201 f) tratamiento de aminas primarias y secundarias con un isocianato, cloruro de ácido (u otro derivado de ácido carboxílico activado), cloroformiato de alquilo/arilo o cloruro de sulfonilo para proporcionar los correspondientes urea, amida, carbamato o sulfonamida; g) aminación reductora de una amina primaria o secundaria usando $R^1CH(O)$; y h) tratamiento de alcoholes con un isocianato, cloruro de ácido (u otro derivado de ácido carboxílico activado), cloroformiato de alquilo/arilo o cloruro de sulfonilo para proporcionar los correspondientes carbamato, éster, carbonato o éster de ácido sulfónico.

Los compuestos de la presente invención pueden tener átomos de carbono asimétrico. Las mezclas diastereoméricas se pueden separar en sus diastereómeros individuales en base a sus diferencias físicas y químicas mediante procedimientos conocidos por los expertos en la técnica, por ejemplo, mediante cromatografía o cristalización fraccionada. Los enantiómeros se pueden separar convirtiendo las mezclas enantioméricas en una mezcla diastereomérica mediante reacción con un compuesto ópticamente activo apropiado (por ejemplo, alcohol), separando los disatereómeros y convirtiendo (por ejemplo, hidrolizando) los diastereómeros individuales en los enantiómeros puros correspondientes; o mediante separación cromatográfica usando una fase quiral estacionaria y móvil. Todos estos isómeros, incluyendo las mezclas diastereoméricas y enantiómeros puros se consideran como parte de la invención.

Los compuestos de fórmula (I) que son básicos por naturaleza son capaces de formar una amplia diversidad de sales diferentes con diversos ácidos inorgánicos y orgánicos. Aunque dichas sales deben ser farmacéuticamente aceptables para la administración a animales, a menudo es

deseable en la práctica aislar inicialmente el compuesto de fórmula (I) a partir de la mezcla de reacción como una sal farmacéuticamente aceptable y después convertir simplemente este último en el compuesto de base libre mediante tratamiento con un reactivo alcalino y posteriormente convertir la última base libre en una sal de adición de ácido farmacéuticamente aceptable. Las sales de adición de ácido de los compuestos básicos de esta invención se preparan fácilmente tratando el compuesto básico con una cantidad sustancialmente equivalente del ácido mineral u orgánico elegido en un medio disolvente acuoso o en un disolvente orgánico adecuado, tal como metanol o etanol. Tras la evaporación cuidadosa del disolvente, se obtiene fácilmente el sólido deseado. La sal de ácido deseada también se puede precipitar a partir de una solución de la base libre en un disolvente orgánico mediante la adición a la solución de un ácido mineral u orgánico apropiado.

Los compuestos de fórmula (I) que son ácidos por naturaleza son capaces de formar sales básicas con diversos cationes farmacológicamente aceptables. Los ejemplos de dichas sales incluyen las sales de metales alcalinos o metales alcalinotérreos y particularmente, las sales de sodio y potasio. Todas estas sales se preparan mediante técnicas convencionales. Las bases químicas que se usan como reactivos para preparar las sales farmacéuticamente aceptables de esta invención son las que forman sales básicas no tóxicas con los compuestos de fórmula (I). Dichas sales básicas no tóxicas incluyen las derivadas de dichos cationes farmacológicamente aceptables tales como sodio, potasio, calcio y magnesio, etc. Estas sales se pueden preparar fácilmente tratando los compuestos ácidos correspondientes con una solución acuosa que contiene los cationes farmacéuticamente

aceptables deseados, y después evaporando la solución resultante hasta sequedad, preferiblemente a presión reducida. Como alternativa, también se pueden preparar mezclando soluciones alcanolicas inferiores de los compuestos ácidos y el alcóxido de metal alcalino deseado conjuntamente, y después evaporando la solución resultante hasta sequedad de la misma manera que antes. En cualquier caso, se emplean preferiblemente cantidades estequiométricas de los reactivos con el fin de asegurar la finalización de la reacción y máximo rendimiento del producto final deseado.

Los compuestos de la presente invención son moduladores de PPAR, preferiblemente PPAR γ y α. Los compuestos de la presente invención pueden modular los procedimientos mediados por PPAR-γ, que se refiere a procesos corporales biológicos, fisiológicos, endocrinológicos y otros que están mediados por un receptor o combinaciones de receptores que son sensibles a los agonistas PPAR descritos en esta memoria descriptiva (por ejemplo, diabetes, hiperlipidemia, obesidad, tolerancia a la glucosa alterada, hipertensión, hígado graso, complicaciones diabéticas (por ejemplo, retinopatía, neuropatía, neurosis, cataratas y enfermedades de las arterias coronarias y similares), arteriosclerosis, diabetes de embarazo, síndrome de ovario poliquístico, enfermedades cardiovasculares (por ejemplo, enfermedad cardiaca isquémica y similares), lesión celular (por ejemplo, lesión cerebral inducida por accidentes cerebrovasculares y similares) inducida por aterosclerosis o enfermedad cardiaca isquémica, gota, enfermedades inflamatorias (por ejemplo, artrosteitis, dolor, pirexia, artritis reumatoide, enteritis inflamatoria, acné, quemaduras solares, psoriasis, eccema, alergosis, asma, úlcera GI, caquexia, enfermedades autoinmunes, pancreatitis y

similares), cáncer, osteoporosis y cataratas. La modulación de tales procesos se puede lograr *in vitro* o *in vivo*. La modulación *in vivo* se puede llevar a cabo en un amplio intervalo de sujetos, tales como, por ejemplo, seres humanos, roedores, ovejas, cerdos, vacas, y similares.

Los compuestos de la presente invención también pueden ser útiles en el tratamiento de otros síndromes metabólicos asociados a la utilización alterada de glucosa y resistencia a la insulina incluidos complicaciones de fase última de NIDDM, tales como angiopatía diabética, aterosclesosis, nefropatía diabética, neuropatía diabética, y complicaciones diabéticas oculares tales como retinopatía, formación de cataratas y glaucoma, y muchas otras afecciones unidas a NIDDM, incluyendo dislipidemia, resistencia a la insulina inducida por glucocorticoides, dislipidemia, síndrome de ovario poliquístico, obesidad, hiperglucemia, hiperlipidemia, hipercolesteremia, hipertrigliceridemia, hiperinsulinemia, e hipertensión. Las definiciones breves de estas definiciones están disponibles en cualquier diccionario médico, por ejemplo Stedman's Medical Dictionary (ed. X).

La actividad *in vitro* de los compuestos de fórmula (I) se puede determinar mediante el siguiente procedimiento.

Ensayos de análisis centelleo por proximidad (abreviadamente en inglés SPA)

En el ensayo de SPA, darglitazona (para PPAR-γ) o GW2331 (para PPAR-α) marcada con 3H se une a la proteína de PPAR capturada sobre perlas de polilisina de SPA y genera señal de conteo radiactivo que se puede detectar mediante TopCounts (Packard). El ligando marcado con 3H unido a PPAR se puede desplazar mediante un compuesto no marcado. La Ki del compuesto se puede después determinar mediante el grado de desplazamiento

a diversas concentraciones del compuesto.

Reactivos:

Perlas de polilisina de SPA, que se pueden comprar en Amersham Bioscience.

Darglitazona marcada con 3H para PPAR-γ

GW2331 marcada con 3H para PPAR-α

Proteínas de PPAR.

Tampón – PBS, glicerol al 10%, betamercaptoetanol 14 mM.

Todos los compuestos de la presente invención que se ensayaron tienen valores de Ki en al menos uno de los ensayos de SPA anteriores de entre 0,3 nM a 30 μM. Ciertos grupos preferidos de los compuestos poseen selectividad diferencial hacia los diversos PPAR. Un grupo de los compuestos preferidos posee actividad selectiva hacia PPAR-α sobre PPAR-γ. Otro grupo preferido de los compuestos posee actividad selectiva hacia PPAR-γ sobre PPAR-α. Otro grupo preferido de compuestos posee actividad selectiva hacia tanto PPAR-α como PPAR-γ sobre PPAR-δ. Otro grupo preferido de compuestos posee actividad selectiva hacia PPAR- δ sobre tanto PPAR-α como PPAR- γ.

Los compuestos de ácidos carboxílicos alfa sustituidos de fórmula (I) se pueden proporcionar en formulaciones tópicas, orales y parenterales adecuadas para uso en el tratamiento de enfermedades mediadas por PPAR. Los compuestos de la presente invención se pueden administrar oralmente en forma de comprimidos o cápsulas, en forma de suspensiones oleosas o acuosas, grageas, trociscos, polvos, gránulos, emulsiones, jarabes elixires. Las composiciones para uso oral pueden incluir uno o más agentes para

aromatizar, edulcorar, colorear y conservar con el fin de producir preparaciones farmacéuticamente elegantes y palatables. Los comprimidos pueden contener excipientes farmacéuticamente aceptables como ayuda en la fabricación de tales comprimidos. Como es convencional en la técnica de estos comprimidos se pueden recubrir con un revestimiento entérico farmacéuticamente aceptable, tales como monoestearato de glicerilo o diestearato de glicerilo, para retrasar la desintegración y absorción en el tracto gastrointestinal con el fin de proporcionar una acción sostenida durante un período más largo.

Las formulaciones para uso oral pueden estar en la forma de cápsulas duras de gelatina en las que el ingrediente activo se mezcla con un diluyente sólido inerte, por ejemplo, carbonato cálcico, fosfato potásico o caolín. Pueden estar en forma de cápsulas blandas de gelatina en las que el ingrediente activo se mezcla con agua o un medio oleoso, tales como aceite de cacahuete, aceite de parafina o aceite de oliva.

Las suspensiones acuosas normalmente contienen ingredientes activos en mezcla con excipientes adecuados para la fabricación de una suspensión acuosa. Dichos excipientes pueden ser un agente de suspensión, tal como carboximetilcelulosa de sodio, metilcelulosa, hidroxipropilmetilcelulosa, alginato de sodio, polivinilpirrolidona, goma tragacanto y goma arábiga; un agente de dispersión o humectante que pueden ser un fosfátido de origen natural tal como lecitina, un producto de condensación de óxido de etileno y un ácido graso de cadena larga, por ejemplo estearato de polioxietileno, un producto de condensación de óxido de etileno y un alcohol alifático de cadena larga, un producto de condensación de óxido de etileno y un alcohol alifático de cadena larga tal como heptadecaetilenoxicetanol, un producto de condensación de

óxido de etileno y un éster parcial derivado de un ácido graso y hexitol tal como monooleato de sorbitol polioxietilenado o un anhídrido de hexitol de ácido graso tal como monooleato de sorbitán polioxietilenado.

Las composiciones farmacéuticas pueden estar en forma de una suspensión estéril inyectable acuosa u oleaginosa. Esa suspensión se puede formular según procedimientos conocidos usando los agentes de dispersión o humectantes adecuados y agentes de suspensión que se han mencionado anteriormente. La preparación inyectable estéril también se puede formular en forma de una suspensión en un diluyente o disolvente no tóxico, parenteralmente aceptable, por ejemplo en forma de una solución en 1,3-butanodiol. Entre los vehículos y disolventes aceptables que se pueden emplear están agua, solución Ringer y solución isotónica de cloruro sódico. Para este propósito se puede emplear cualquier aceite blando estable incluyendo mono- o diglicéridos sintéticos. Además de los ácidos grasos tales como el ácido oleico encuentran uso en la preparación de inyectables.

Los compuestos de ácidos carboxílicos alfa sustituidos de fórmula (I) también se pueden administrar en forma de supositorios para administración rectal del fármaco. Estas composiciones se pueden preparar mezclando el fármaco con un excipiente no irritante adecuado que es sólido a aproximadamente la temperatura ambiente pero líquido a temperatura rectal y por lo tanto se funden en el recto para liberar el fármaco. Dichos materiales incluyen manteca de cacao y otros glicéridos.

Para preparaciones de uso tópico, se emplean por ejemplo, cremas, pomadas, gelatinas, soluciones o suspensiones, que contienen los compuestos de la presente invención.

Los compuestos de ácidos carboxílicos alfa sustituidos de fórmula (I) también se pueden administrar en forma de sistemas de administración de liposomas tales como vesículas unilamelares pequeñas, vesículas unilamelares grandes y vesículas multilamelares. Los liposomas se pueden formar a partir de una diversidad de fosfolípidos, tales como colesterol, estearilamina o fosfatidilcolinas.

Los niveles de dosificación de los compuestos de la presente invención son del orden de aproximadamente 0,5 mg/kg de peso corporal a aproximadamente 100 mg/kg de peso corporal. Una tasa de dosificación preferida está entre aproximadamente 30 mg/kg de peso corporal y aproximadamente 100 mg/kg de peso corporal. Sin embargo, se entenderá que el nivel específico de dosificación para cualquier paciente particular dependerá de numerosos factores incluyendo la actividad del compuesto particular que se está administrando, la edad, peso corporal, salud general, sexo, dieta, tiempo de administración, vía de administración, velocidad de excreción, combinación de fármacos y la gravedad de la enfermedad particular que se somete a terapia. Para potenciar la actividad terapéutica de los presentes compuestos se pueden administrar simultáneamente con otros compuestos antidiabéticos oralmente activos tales como las sulfonilureas, por ejemplo, la tolbutamida y similares.

Se conocen los procedimientos de preparación de diversas composiciones farmacéuticas con una cantidad específica de compuesto activo, o serán evidentes para los expertos en esta técnica. Para ejemplos, véase Remington's Pharmaceutical Sciences, Mack Publishing Company, Easter, Pa., edición 15 (1975).

Los ejemplos y preparaciones proporcionadas más adelante además ilustran y ejemplifican los compuestos de la presente invención de la presente invención y los procedimientos de preparación de de dichos compuestos. Se entenderá que el alcance de la presente invención no está limitado de ninguna forma por el alcance de los ejemplos y las preparaciones siguientes. En los siguientes ejemplos las moléculas con un único centro quiral, salvo que se indique otra cosa, existen como una mezcla racémica. Las moléculas con dos o más centros quirales, salvo que se indique otra cosa, existen como mezcla racémica de diastereómeros. Los enantiómeros/diastereómeros individuales se pueden obtener mediante procedimientos conocidos por los expertos en la técnica.

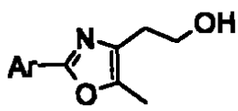
Cuando se menciona la cromatografía de HPLC en las preparaciones y los ejemplos más adelante, las condiciones generales usadas, salvo que se indique otra cosa, son como sigue. La columna usada es una columna ZORBAX™ RXC18 (fabricada por Hewlett Packard) de 150 mm de distancia y 4,6 mm de diámetro interior. Las muestras se procesan sobre un sistema de Hewlett Packard – 1100 system A. Se usa el procedimiento de disolventes en gradiente utilizando tampón acetato amónico al 100 por ciento / ácido acético (0,2 M) hasta acetonitrilo al 100 por ciento durante 10 minutos. Después el sistema sigue adelante sobre un ciclo de agua con acetonitrilo al 100 por ciento durante 1,5 minutos y después solución de tampón al 100 por ciento durante 3 minutos. El caudal durante este período es constante de 3 ml/minuto.

En los ejemplos y preparaciones siguientes, "Et" significa etilo, "AC" siginifica acetilo, "Me" significa metilo, "ETOAC" o "ETOAc" significa acetato de etilo, "THF" significa tetrahidrofurano, y "BU" significa butilo.

Condiciones de cromatografía con fluido supercrítico quiral (abreviadamente SFC)

Los enantiómeros individuales de ciertos compuestos racémicos se obtuvieron mediante SFC usando una columna quiralpak AD-H a 14.000 kPa y 2,5 mL/min, columna quiralpak AS-H a 14.000 kPa y 2,5 mL/min, columna quiralpak OJ-H a 14.000 kPa y 2,5 mL/min.

A lo largo de las secciones siguientes, los compuestos de fórmula general más adelante se prepararon mediante procedimientos análogos a los descritos en Heterocycles, 2001, **55** (4), 689 – 703.



Ejemplo A – 1

Ácido 2-metil-2-({3'-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]-1,1'-bifenil-3-il}oxi)propanoico

A una solución de 2-metil-2-({3'-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]-1,1'-bifenil-3- il}oxi)propanoato de metilo (0,89 g, 1,76 mmoles) en metanol (20 mL) se añadió agua (2,6 mL) y carbonato potásico (0,73 g, 2,0 equiv.). Después la mezcla se calentó a reflujo durante 5 horas y se dejó enfriar hasta

temperatura ambiente. Después la solución se vertió en agua, se acidificó hasta pH 2 con ácido clorhídrico 1 N y se extrajo con acetato de etilo (3 x 30 mL). Los extractos orgánicos combinados se lavaron con cloruro sódico acuoso saturado, se secaron (sulfato sódico anhidro), se filtraron y se concentraron hasta sequedad para proporcionar el compuesto del título en forma de un sólido cristalino blanco (0,6 g, 70%).

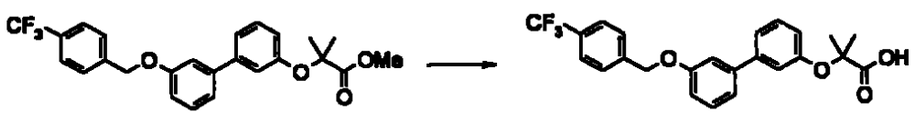
Análisis elemental: calculado para $C_{28}H_{27}NO_5$ C 73,51, H 5,95, N 3,06. Encontrado: C 73,26, H 6,08, N 3,06.

EMBR: 458 $(M + H)^+$.

^{1}H RMN ($CDCl_3$, 400 MHz): 7,97 (2H, dd, *J* = 3,0, 6,6 Hz), 7,43 (2H, d, *J* = 2,8 Hz), 7,41 (1H, s), 7,31 (2H, dd, *J* = 8,0 Hz), 7,23 (2H, d, *J* = 8,6 Hz), 7,17 (1H, d, *J* = 7,6 Hz), 7,12 (1H, s a), 6,93 (1H, dd, *J* = 1,4, 8,2, Hz), 6,87 (1H, dd, *J* = 2,0, 8,1 Hz), 4,29 (1H, t, *J* = 7,7 Hz), 3,07 (2H, t, *J* = 7,7 Hz), 2,40 (3H, s), 1,63 (6H, s).

Ejemplo A – 2

Ácido 2-metil-2-[(3'-{[4-(trifluorometil)bencil]oxi}-1,1'-bifenil-3- il)oxi]propanoico

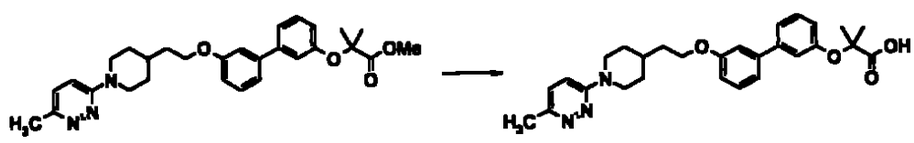


Siguiendo el procedimiento descrito en el ejemplo A – 1, partiendo de 2-metil-2-[(3'-{[4-(trifluorometil)bencil]oxi}-1,1'-bifenil-3-il)oxi]propanoato de metilo, se produjo el compuesto del título.

EMBR: 431 $(M + H)^+$.

Ejemplo A – 3

Ácido 2-metil-2-[(3'-{2-[1-(6-metilpiridazin-3-il)piperidin-4-il]etoxi}-1,1'-bifenil-3-il)oxi]propanoico



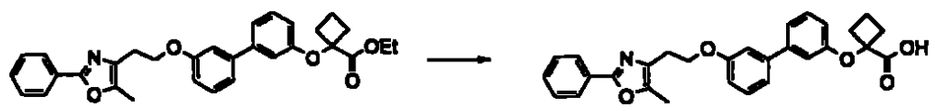
Siguiendo el procedimiento descrito en el ejemplo A – 1, partiendo de 2-metil-2-[(3'-{2-[1-(6-metilpiridazin-3-il)piperidin-4-il]etoxi}-1,1'-bifenil-3-il)oxi]propanoato de metilo, se produjo el compuesto del título en forma de un sólido cristalino amarillo claro.

EMBR: 477 $(M + H)^+$.

^{1}H RMN ($CDCl_3$, 400 MHz): 7,27 (2H, c, J = 8,1 Hz), 7,20 – 7,18 (2H, m), 7,12 (1H, d a, J = 7,8 Hz), 7,08 – 7,06 (2H, m), 6,94 – 6,93 (1H, m), 6,91 – 6,90 (1H, m), 6,84 (1H, dd, J = 2,0, 7,8 Hz), 4,25 (2H, d a, J = 13,1 Hz), 4,04 (2H, t, J = 6,1 Hz), 2,88 (2H, t, J = 13,4 Hz), 2,48 (3H, s), 1,80 – 1,70 (5H, m), 1,65 (6H, s), 1,33 – 1,27 (2H, m).

Ejemplo A – 4

Ácido 1-({3'-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]-1,1'-bifenil-3-il}oxi)ciclobutanocarboxílico



A una solución de 1-({3'-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]-1,1'-bifenil-3-il}oxi)ciclobutanocarboxilato de etilo (0,138 g, 0,278 mmoles) en tetrahidrofurano (3 mL) y metanol (1 mL) se añadió hidróxido de litio acuoso (0,28 mL). La mezcla resultante se agitó a temperatura ambiente durante 16 horas. Se añadieron agua (5 mL) y éter dietílico (10 mL) y la solución resultante se agitó durante 10 minutos. La fase etérea se retiró y la fase acuosa se acidificó hasta pH 2 con ácido clorhídrico 1 N a 0°C y se agitó durante 20 minutos. Se recogió el precipitado blanco mediante filtración y se lavó con agua enfriada con hielo. Después de secar a 40°C a alto vacío el compuesto del título se produjo en forma de un sólido cristalino blanco (0,091 g, 70%).

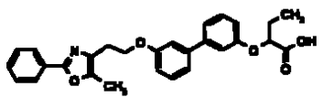
Análisis elemental: calculado para $C_{29}H_{27}NO_5$ 0,15LiCl C 73,18, H 5,72, N 2,94. Encontrado: C 73,08, H 5,67, N 2,93.

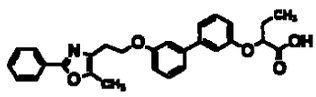
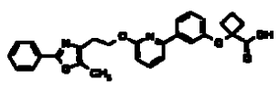
EMBR: 471 $(M + H)^+$.

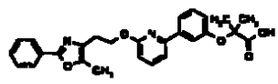
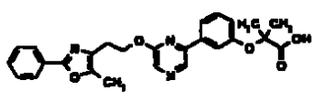
^1H RMN ($CDCl_3$, 400 MHz): 8,03 – 8.00 (2H, m), 7,43 (3H, t, J = 3,3 Hz), 7,30 (2H, t, J = 7,8 Hz), 7,16 (2H, d, J = 6,8 Hz), 7,09 (1H, t, J = 2,3 Hz), 6,91 – 6,85 (3H, m), 4,27 (2H, t, J = 7,8 Hz), 3,06 (3H, t, J = 8,1 Hz), 2,83 – 2,76 (2H, m), 2,53 – 2,46 (2H, m), 2,40 (3H, s), 2,06 – 1,97 (2H, m).

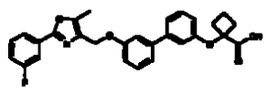
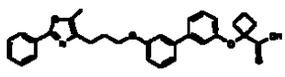
Ejemplo A – 5 a A – 28

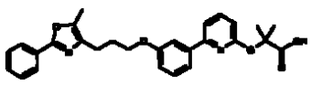
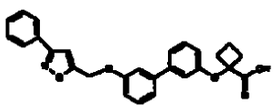
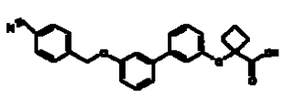
Los ejemplos A – 5 a A – 28 se prepararon usando procedimientos análogos a los descritos para el ejemplo A – 4

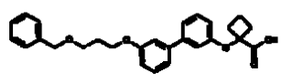
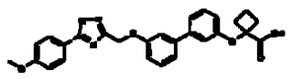
Ej. nº	Estructura	^{1}H RMN	EM (m/z) (BR o AR)	Análisis
A – 5		($CDCL_3$, 400 MHz): 7,95 (2H, dd, *J* = 2,9, 6,7 Hz), 7,38 – 7,35 (3H, m), 7,29 – 7,22 (2H, m), 7,13 – 7,10 (3H, m), 7,07 (1H, t, *J* = 2,3 Hz), 6,91 – 6,88 (1H, m), 6,81 (1H, dd, *J* = 1,8, 8,3 Hz), 4,57 (1H, t, *J* = 6,2 Hz), 4,23 (2H, t, *J* = 7,7 Hz), 3,05 – 2,92 (2H, m), 2,34 (3H, s), 2,03 – 1,96 (2H, m), 1,06 (3H, t, *J* = 7,5 Hz).	para BR 458 $(M+H)^+$.	Calculado para $C_{28}H_{27}NO_5$ 0,41 H_2O C 72,34, H 6,03, N 3,01. Encontrado: C 72,33, H 6,01, N 2,95

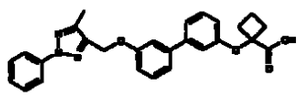
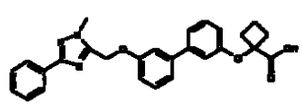
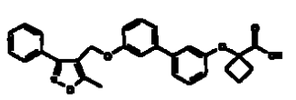
A – 6		(DMSO-d_6, 400 MHz): 7,91 (2H, dd, *J* = 1,8, 7,6 Hz), 7,73 (1H, t, *J* = 7,8 Hz), 7,52 – 7,44 (6H, m), 7,25 (1H, t, *J* = 8,0 Hz), 6,83 (1H, dd, *J* = 2,0, 8,1 Hz), 6,72 (1H, d, *J* = 8,1 Hz), 4,61 (2H, t, *J* = 6,7 Hz), 4,11 (1H, t, *J* = 6,3 Hz), 2,98 (2H, t, *J* = 6,7 Hz), 2,32 (3H, s), 1,84 – 1,69 (2H, m), 0,95 (3H, t, *J* = 7,3 Hz).	para BR 459 $(M+H)^+$.	Calculado para $C_{27}H_{25}LiN_2O_5$ 2,32 H_2O C 64,82, H 6,17, N 5,60. Encontrado: C 64,83, H 5,89, N 5,52
A – 7		($CDCl_3$, 400 MHz): 8,02 – 8,00 (2H, m), 7,65 – 7,64 (1H, m), 7,61 (1H, m), 7,45 – 7,42 (3H, m), 7,40 – 7,30 (3H, m), 7,05 (1H, ddd, *J* = 1,0, 2,5, 7,8 Hz), 6,65 (1H, d, *J* = 8,1 Hz), 4,74 – 4,69 (2H, m), 3,10 – 3,07 (2H, m), 2,83 – 2,76 (2H, m), 2,47 – 2,38 (2H, m), 2,40 (3H, s), 2,09 –	para BR 471 $(M+H)^+$.	Calculado para $C_{28}H_{28}N_2O_5$ 0,09 LiCl C 70,89, H 5,52, N 5,90. Encontrado: C 70,94, H 5,65, N 5,93

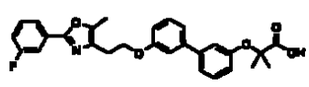
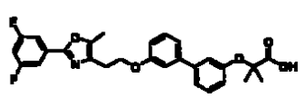
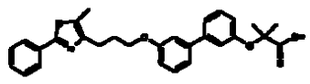
		1,95 (2H, m).		
A – 8		($CDCl_3$, 400 MHz): 8,11 (1H, dd, J = 1,5, 2,5 Hz), 8,00 – 7,97 (2H, m), 7,62 (1H, t, J = 7,6 Hz), 7,46 – 7,41 (4H, m), 7,35 (1H, d, J = 7,3 Hz), 7,31 (1H, t, J = 7,8 Hz), 7,00 (1H, ddd, J = 1,0, 2,8, 8,1 Hz), 6,65 (1H, d, J = 8,3 Hz), 4,74 – 4,69 (2H, m), 3,16 – 3,12 (2H, m), 2,41 (3H, s), 1,63 (6H, s).	para BR 459 $(M+H)^+$.	
A – 9		($CDCl_3$, 400 MHz): 8,63 (1H, s a), 8,13 (1H, s a), 8,06 (1H, dd, J = 1,3, 2,5 Hz), 7,99 – 7,96 (2H, m), 7,52 (1H, d, J = 7,8 Hz), 7,46 – 7,42 (3H, m), 7,35 (1H, t, J = 7,8 Hz), 7,04 (1H, t, J = 7,8 Hz), 4,72 – 4,68 (2H, m), 3,16 – 3,12 (2H, m), 2,43 (3H, s), 1,63 (6H, s).	para BR 460 $(M+H)^+$.	Calculado para $C_{28}H_{25}N_3O_5$ 0,47 H_2O C 66,73, H 5,59, N 8,98. Encontrado: C 66,69, H 5,48, N 8,96.

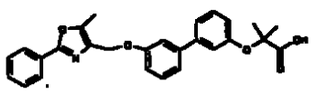
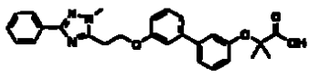
A – 10		^{1}H RMN ($CDCl_3$, 400 MHz): 1,91 – 2,02 (m, 2 H), 2,24 – 2,31 (m, 3 H), 2,38 – 2,49 (m, 2 H), 2,75 (td, 2 H), 2,86 (t, 2 H), 4,04 (t, 2 H), 6,58 (dd, 1 H), 6,75 – 6,86 (m, 3 H), 7,04 (d, 1 H), 7,16 – 7,22 (m, 2 H), 7,30 – 7,38 (m, 3 H), 7,90 (dd, 2 H)	EMBR (*m/z*) 470 $(M+H)^+$.	
A – 11		^{1}H RMN ($CDCl_3$, 400 MHz): 1,83 – 2,05 (m, 2 H), 2,51 (s, 3 H), 2,50 – 2,58 (m, 2 H), 2,75 – 2,83 (m, 2 H), 5,02 (s, 2 H), 6,52 (m, 1 H), 6,96 – 7,56 (m, 9 H), 7,73 – 7,86 (m, 2 H).		
A – 12		^{1}H RMN ($CDCl_3$, 400 MHz): 1,97 – 2,07 (m, 2 H), 2,13 – 2,23 (m, 2 H), 2,29 (s, 3 H), 2,45 – 2,54 (m, 2 H), 2,70 – 2,81 (m, 4 H), 4,21 (c, 2 H), 6,63 – 6,65 (m, 1	EMBR (*m/z*) 484,5 $(M+H)^+$.	

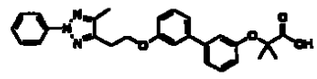
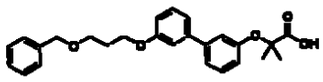
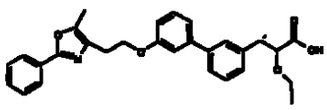
		H), 7,07 – 7,18 (m, 2 H), 7,24 – 7,34 (m, 4 H), 7,37 – 7,45 (m, 4 H), 7,98 (dd, 2 H).		
A – 13		^{1}H RMN ($CDCl_3$, 400 MHz): 1,61 (s, 6 H), 2,35 (s, 3 H), 2,78 – 2,89 (m, 4 H), 4,23 – 4,31 (m, 2 H), 6,77 (d, 2 H), 7,15 (d, 4 H), 7,36 – 7,45 (m, 4 H), 7,97 (dd, 2 H).	EMBR (*m/z*) 473,5 $(M+H)^+$.	
A – 14		^{1}H RMN ($CDCL_3$, 400 MHz): 1,99 – 2,11 (m, 2 H), 2,51 (dc, 2 H), 2,77 – 2,85 (m, 2 H), 5,25 (s, 2 H), 6,65 – 6,72 (m, 2 H), 6,94 – 6,99 (m, 2 H), 7,15 – 7,22 (m, 2 H), 7,35 (t, 2 H), 7,42 – 7,51 (m, 2 H), 7,80 (dd, 4 H).	EMBR (*m/z*) 443,0 $(M+H)^+$.	
A – 15		^{1}H RMN ($CDCl_3$, 400 MHz): 1,98 – 2,08 (m, 2 H), 2,45 – 2,55 (m, 2 H), 2,74 – 2,83 (m, 2	EMBR (*m/z*) 423,0 $(M+H)^+$.	

		H), 5,18 (s, 2 H), 6,91 – 6,98 (m, 1 H), 7,13 – 7,21 (m, 2 H), 7,26 – 7,37 (m, 5 H), 7,56 – 7,63 (m, 2 H), 7,69 (d, 2 H).		
A – 16		^{1}H RMN ($CDCl_3$, 400 MHz): 1,96 – 2,07 (m, 2 H), 2,48 – 2,51 (m, 2 H), 2,73 – 2,82 (m, 2 H), 4,31 – 4,40 (m, 4 H), 6,63 (dd, 1 H), 6,92 – 7,00 (m, 5 H), 7,13 – 7,21 (m, 3 H), 7,25 – 7,36 (m, 4 H)	EMBR (*m/z*) 423,0 $(M+H)^+$.	
A – 17		^{1}H RMN ($CDCl_3$, 400 MHz): 1,96 – 2,07 (m, 2 H), 2,44 – 2,55 (m, 2 H), 2,74 – 2,82 (m, 2 H), 3,89 (s, 1 H), 5,25 – 5,31 (s, 2 H), 6,63 – 6,65 (m, 1 H), 7,00 – 7,10 (m, 4 H), 7,17 (t, 2 H), 7,23 – 7,31 (m, 4 H), 8,12 (d, 2 H).	EMBR (*m/z*) 473,5 $(M+H)^+$.	

A – 18		^{1}H RMN ($CDCl_3$, 400 MHz): 2,02 – 2,14 (m, 2 H), 2,44 – 2,54 (m, 5 H), 2,75 – 2,86 (m, 2 H), 5,26 (s, 2 H), 6,95 – 7,05 (m, 1 H), 7,16 – 7,23 (m, 2 H), 7,25 – 7,36 (m, 6 H), 7,46 (t, 2 H), 8,02 (d, 2 H).	EMBR (*m/z*) 456,5 $(M+H)^+$.	
A – 19		^{1}H RMN ($CDCl_3$, 400 MHz): 1,96 – 2,07 (m, 2 H), 2,44 – 2,54 (m, 5 H), 2,74 – 2,82 (m, 2 H), 5,25 (s, 2 H), 6,96 – 7,04 (m, 1 H), 7,16 (d, 2 H), 7,22 – 7,28 (m, 2 H), 7,32 (td, 4 H), 7,42 – 7,49 (m, 2 H), 7,99 – 8,05 (m, 2 H).	EMBR (*m/z*) 456,1 $(M+H)^+$.	
A – 20		^{1}H RMN ($CDCl_3$, 400 MHz): 1,97 – 2,07 (m, 2 H), 2,52 (s, 3 H), 2,64 – 2,65 (m, 2 H), 2,74 – 2,82 (m, 2 H), 4,89 (s, 2 H), 6,68 – 6,70 (m, 1 H), 6,83 – 6,85 (m, 2	EMBR (*m/z*) 456,2 $(M+H)^+$.	

		H), 7,24 – 7,30 (m, 3 H), 7,41 – 7,47 (m, 3 H), 7,58 – 7,62 (m, 2 H), 7,66 – 7,68 (m, 2 H).		
A – 21		^{1}H RMN ($CDCl_3$, 400 MHz): 1,56 – 1,65 (m, 6 H), 2,43 (s, 3 H), 3,09 (t, 2 H), 4,33 (t, 2 H), 6,86 – 6,96 (m, 2 H), 7,11 – 7,19 (m, 2 H), 7,20 – 7,26 (m, 4 H), 7,32 (t, 2 H), 7,41 (td, 1 H), 7,70 (ddd, 1 H), 7,81 (d, 1 H).	EMBR (*m/z*) 476 $(M+H)^+$.	
A – 22		^{1}H RMN ($CDCl_3$, 400 MHz): 1,64 (s, 6 H), 2,41 (s, 3 H), 3,06 (t, 2 H), 4,31 (t, 2 H), .6,88 (dd, 3 H), 7,04 – 7,13 (m, 1 H), 7,14 – 7,23 (m, 2 H), 7,23 – 7,34 (m, 3 H), 7,52 (dd, 2 H).	EMBR (*m/z*) 494 $(M+H)^+$.	
A – 23		^{1}H RMN ($CDCl_3$, 400 MHz): 1,71 (s, 6 H),	EMBR (*m/z*)	

		2,10 – 2,22 (m, 2 H), 2,35 (s, 3 H), 2,67 – 2,77 (m, 2 H), 3,99 – 4,09 (m, 2 H), 6,67 – 6,69 (m, 2 H), 7,04 – 7,13 (m, 2 H), 7,20 – 7,32 (m, 4 H), 7,37 – 7,44 (m, 2 H), 7,92 – 8,02 (m, 3 H).	472,5 $(M+H)^+$.	
A – 24		^{1}H RMN ($CDCl_3$, 400 MHz): 1,76 (s, 6 H), 2,49 (s, 3 H), 5,16 (s, 2 H), 7,07 – 7,19 (m, 2 H), 7,23 (t, 1 H), 7,32 (td, 4 H), 7,36 – 7,47 (m, 4 H), 7,98 (dd, 2 H).	EMBR (*m/z*) 444,5 $(M+H)^+$.	
A – 25		^{1}H RMN ($CDCl_3$, 400 MHz): 1,58 (s, 6 H), 3,35 (t, 2 H), 3,99 (s, 3 H), 4,40 (t, 2 H), 6,80 (d, 1 H), 6,81 (dd, 1 H), 7,00 (d, 1 H), 7,11 – 7,20 (m, 3 H), 7,25 (m, 2 H), 7,33 – 7,38 (m, 3 H), 7,92 – 8,00 (m, 2 H).	EMBR (*m/z*) 458 $(M+H)^+$.	

A – 26		^{1}H RMN ($CDCl_3$, 400 MHz): 1,56 (s, 6 H), 2,31 (s, 3 H), 3,11 (t, 2 H), 4,25 (t, 2 H), 6,81 (m, 2 H), 6,96 (s, 1 H), 7,06 (m, 2 H), 7,20 (m, 4 H), 7,30 (t, 3 H), 7,82 (d, 2 H).	EMBR (*m/z*) 458 $(M+H)^+$.	
A – 27		^{1}H RMN ($CDCl_3$, 400 MHz): 1,62 (s, 6 H), 2,07 – 2,15 (m, 2 H), 3,60 – 3,71 (m, 2 H), 4,13 (c, 2 H), 4,53 (s, 2 H), 6,83 – 6,93 (m, 2 H), 7,01 – 7,09 (m, 1 H), 7,12 (d, 1 H), 7,14 – 7,20 (m, 1 H), 7,30 (ddd, 8 H).	EMBR (*m/z*) 421 $(M+H)^+$.	
A – 28		^{1}H RMN ($CDCl_3$, 400 MHz): 1,18 (t, 3 H), 2,43 (s, 3 H), 2,96 – 3,08 (m, 4 H), 3,32 – 3,35 (m, 2 H), 3,62 – 3,65 (m, 1 H), 4,24 – 4,33 (m, 2 H), 7,07 – 7,19 (m, 2 H), 7,23 (t, 1	EMBR (*m/z*) 472,5 $(M+H)^+$.	

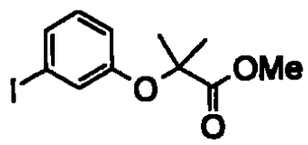
		H), 7,32 (td, 4 H), 7,36 – 7,47 (m, 4 H), 7,98 (dd, 2 H).		

Preparación de los materiales de partida para los ejemplos A – 1 a A – 28

(preparaciones a – 1 a a – 11

Preparación a – 1

2-(3-yodofenoxi)-2-metilpropanoato de metilo



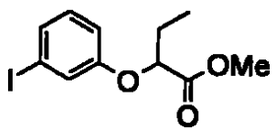
A una solución de 3-yodofenol (1,08 g, 4,9 mmoles) en *N,N*-dimetilformamida (10 mL) se añadió 2-bromo-2-metilpropionato de metilo (0,76 mL, 1,2 equiv) y carbonato de cesio (3,45 g, 2 equiv). La mezcla resultante se calentó a 90ºC durante 24 horas y después se dejó enfriar hasta temperatura ambiente. Se introdujo agua y se extrajo la mezcla con éter dietílico (3 x 20 mL). Se lavaron los compuestos orgánicos combinados con agua y cloruro sódico acuoso saturado, se secaron (sulfato sódico anhidro), se filtraron y se concentraron. El residuo se purificó mediante cromatografía sobre gel se sílice usando 0 – 30% de acetato de etilo en hexanos para proporcionar el compuesto del título (0,83 g, 53%).

EMBR: 321 $(M + H)^+$.

^{1}H RMN ($CDCL_3$, 400 MHz): 7,22 (1H, dt, J = 1,3, 7,8 Hz), 7,12 (1H, dd, J = 1,6, 2,4 Hz), 6,84 (1H, t, J = 8,1 Hz), 6,66 (1H, ddd, J = 0,8, 2,5, 8,3 Hz), 3,66 (3H, s), 1,47 (6H, s).

Preparación a – 2

2-(3-yodofenoxi)butanoato de metilo



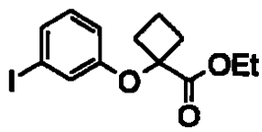
Siguiendo el procedimiento descrito en la preparación a – 1, usando 2-bromopropionato de etilo en lugar de 2-bromo-2-metilpropionato de metilo a temperatura ambiente, el compuesto del título se obtuvo con 93% de rendimiento.

EMBR: 321 $(M + H)^+$.

^1H RMN ($CDCL_3$, 400 MHz): 7,30 (1H, ddd, J = 1,0, 1,5, 7,8 Hz), 7,24 (1H, dd, J = 1,6, 2,4 Hz), 6,97 (1H, dd, J = 7,8, 8,3 Hz), 6,82 (1H, ddd, J = 1,0, 2,5, 8,6 Hz), 4,53 (1H, dd, J = 5,8, 6,6 Hz), 3,75 (3H, s), 2,00 – 1,93 (2H, m), 1,05 (3H, t, J = 7,15 Hz),

Preparación a – 3

1-(3-bromofenoxi)ciclobutanoatocarboxilato de etilo

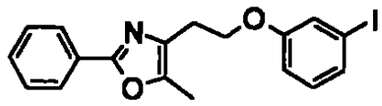


Siguiendo el procedimiento descrito en la preparación a – 1, usando 3-bromofenol y 1-bromociclobutanocarboxilato de etilo como materiales de partida y calentando en una solución de acetonitrilo, el compuesto del título se obtuvo con 56% de rendimiento.

EMBR: 300 $(M + H)^+$.

Preparación a – 4

4-[2-(3-yodofenoxi)etil]-5-metil-2-fenil-1,3-oxazol



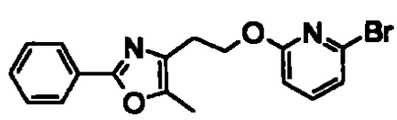
Siguiendo el procedimiento descrito en la preparación a – 1, partiendo de 3-yodofenol y 2-(5-metil-2-fenil-1,3-oxazol-4-il)etil-4-metilbenceno sulfonato a temperatura ambiente, el compuesto del título se obtuvo con 77% de rendimiento en forma de un aceite incoloro.

EMBR: 406 $(M + H)^+$.

^{1}H RMN ($CDCL_3$, 400 MHz): 7,87 (2H, dd, *J* = 1,9, 7,7 Hz), 7,34 – 7,29 (3H, m), 7,15 – 7,13 (2H, m), 6,86 (1H, t, *J* = 8,1 Hz), 6,76 – 6,73 (1H, m), 4,10 (2H, t, *J* = 6,6 Hz), 2,85 (2H, t, *J* = 6,6 Hz), 2,26 (3H, s).

Preparación a – 5

2-Bromo-6-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridina



A una solución de 2-(5-metil-2-fenil-1,3-oxazol-4-il)etanol (1,04 g, 5,1 mmoles) y 2,6-dibromopiridina (1,21 g, 5,1 mmoles) en dioxano anhidro (20 mL)

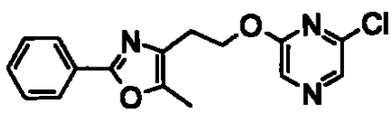
a 0°C se añadió hidruro sódico (60% en aceite, 0,368 g, 3 equiv). La mezcla resultante se agitó a temperatura ambiente durante 16 horas. La mezcla se vertió en agua enfriada con hielo y se extrajo con acetato de etilo (3 x 50 mL). Los extractos orgánicos combinados se lavaron con bicarbonato sódico acuoso saturado y cloruro sódico acuoso saturado, se secaron (sulfato sódico anhidro), se filtraron y se concentraron. El residuo se purificó mediante cromatografía en gel se sílice usando 0 – 50% de acetato de etilo en hexanos para proporcionar el compuesto del título en forma de un sólido cristalino blanco (1,19 g, 65%).

EMBR: 359 $(M + H)^+$.

^{1}H RMN ($CDCL_3$, 400 MHz): 7,97 (2H, dd, J = 1,8, 7,8 Hz), 7,44 – 7,35 (4H, m), 7,03 (1H, d, J = 7,3 Hz), 6,65 (1H, d, J = 8,1 Hz), 4,55 (2H, t, J = 6,8 Hz), 2,97 (2H, t, J = 6,8 Hz), 2,34 (3H, s).

Preparación a – 6

2-Cloro-6-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]pirazina



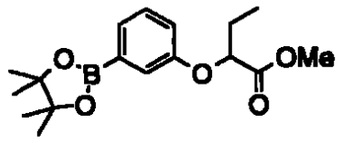
Siguiendo el procedimiento descrito en la preparación a – 5, partiendo de 2-(5-metil-2-fenil-1,3-oxazol-4-il)etanol y 2,6 dicloropirazina, el compuesto del título se obtuvo con 64% de rendimiento.

EMBR: 316 $(M + H)^+$.

^{1}H RMN ($CDCL_3$, 400 MHz): 8,11 (2H, d, J = 10,4 Hz), 7,97 (2H, dd, J = 1,9, 7,7 Hz), 7,44 – 7,39 (3H, m), 4,60 (2H, t, J = 6,7 Hz), 2,99 (2H, t, J = 6,7 Hz), 2,35 (3H, s).

Preparación a – 7

2-[3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenoxi]butanoato de metilo



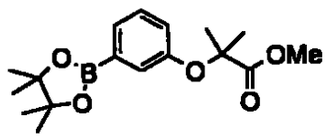
A una solución de 2-(3-yodofenoxi)-2-metilpropanoato de metilo (preparación a – 2) (1,49 g, 4,65 mmoles) en dimetilsulfóxido (40 mL) se añadió acetato potásico (1,37 g, 3 equiv), bis(pinacolato)diboro y una solución de complejo [1,1'-bis(difenilfosfino) – ferroceno]dicloropaladio (II) (0,152 g, 0,04 equiv) en diclorometano. La mezcla resultante se calentó a 80°C durante 16 horas y se dejó enfriar hasta temperatura ambiente. Se introdujo agua y la mezcla se extrajo con éter dietílico (3 x 30 mL). Se lavaron los extractos orgánicos combinados con 5% de bicarbonato sódico acuoso (2 x 50 mL) y cloruro sódico acuoso saturado, se secaron (sulfato sódico anhidro), se filtraron y se concentraron. El residuo se purificó mediante cromatografía en gel se sílice usando 0 – 25% de acetato de etilo en hexanos para proporcionar el compuesto del título (0,92 g, 62%).

EMBR: 321 $(M + H)^+$.

^{1}H RMN ($CDCl_3$, 400 MHz): 7,40 (1H, d, J = 7,3 Hz), 7,32 (1H, d, J = 2,8 Hz), 7,28 (1H, d, J = 8,1 Hz), 6,97 (1H, ddd, J = 1,0, 2,8, 8,1 Hz), 4,64 (1H, t, J = 6,3 Hz), 3,73 (3H, s), 2,01 – 1,94 (2H, m), 1,32 (12H, s), 1,06 (3H, t, J = 7,5 Hz) .

Preparación a – 8

2-metil-2-[3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenoxi]propanoato de metilo



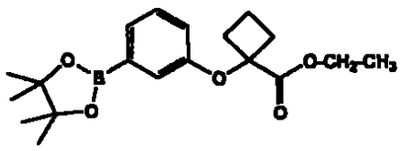
Siguiendo el procedimiento descrito en la preparación a – 7, usando 2-(3-yodofenoxi)-2-metilpropanoato de metilo (preparación 1) como material de partida, el compuesto del título se produjo con 75% de rendimiento.

EMBR: 321 $(M + H)^+$.

^{1}H RMN ($CDCL_3$, 400 MHz): 7,42 (1H, d, J = 7,1 Hz), 7,29 (1H, d, J = 2,8 Hz), 7,22 (1H, t, J = 7,8 Hz), 6,90 (1H, ddd, J = 0,8, 2,8, 8,1 Hz), 3,75 (3H, s), 1,56 (6H, s), 1,30 (12 H, s).

Preparación a – 9

1-[3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenoxi]ciclobutanocarboxilato de etilo

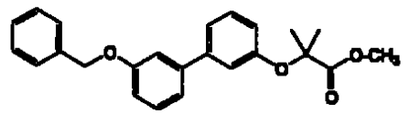


Siguiendo el procedimiento descrito en la prepartación a – 7, usando 1-

(3-bromofenoxi)ciclobutanocarboxilato de etilo (preparación 3) como material de partida, el compuesto del título se produjo con 80% de rendimiento.
EMBR: 347 $(M + H)^+$.

Preparación a – 10

2-[[3'-(benciloxi)-1,1'-bifenil-3-il]oxi]-2-metilpropanoato de metilo

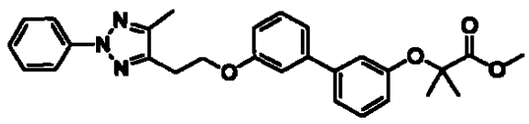


A una solución de 2-(3-yodofenoxi)-2-metilpropanoato de metilo (preparación a – 1) (1,14 g, 3,56 mmoles) en benceno (20 mL) se añadió ácido 3-benciloxifenilbórico (0,89 g, 1,1 equiv), carbonato sódico acuoso 2 M (3,56 mL) y tetraquis(trifenilfosfina) paladio (0) (0,2 g, 0,05 equiv). La mezcla resultante se calentó a reflujo durante 2 horas y se dejó enfriar hasta temperatura ambiente. Se añadió agua y la mezcla se extrajo con éter dietílico (3 x 20 mL). Se lavaron los compuestos orgánicos combinados con 5% de bicarbonato sódico acuoso y cloruro sódico acuoso saturado, se secaron (sulfato sódico anhidro), se filtraron y se concentraron. El residuo se purificó mediante cromatografía en gel se sílice usando 0 – 15% de acetato de etilo en hexanos para proporcionar el compuesto del título en forma de un aceite incoloro (1,08 g, 81%).
EMBR: 377 $(M + H)^+$.

^{1}H RMN ($CDCL_3$, 400 MHz): 7,47 – 7,45 (2H, m), 7,39 (2H, t, *J* = 7,3 Hz), 7,33 (2H, t, *J* = 7,8 Hz), 7,28 (1H, t, *J* = 8,0 Hz), 7,21 (1H, ddd, *J* = 1,0, 1,5, 8,1 Hz), 7,17 (1H, dd, *J* = 1,8, 2,3 Hz), 7,14 (1H, dm, *J* = 7,6 Hz), 7,08 (1H, dd, *J* = 1,8, 2,3 Hz), 6,96 (1H, ddd, *J* = 0,8, 2,5, 8,3 Hz), 6,79 (1H, ddd, *J* = 1,0, 2,5, 8,1 Hz), 5,11 (2H, s), 3,78 (3H, s), 1,62 (6H, s).

Preparación a – 11

2-metil-2-({3'-[2-(5-metil-2-fenil-2H-1,2,3-triazol-4-il)etoxi]bifenil-3-il}oxi)propanoato de metilo



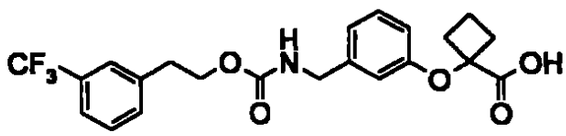
2-(5-metil-2-fenil-2*H*-1,2,3-triazol-4-il)etanol (51 mg, 0,25 mmoles), 2-[(3'-hidroxibifenil-3-il)oxi]-2-metilpropanoato de metilo (86 g mg, 0,30 mmoles), y Ph_3P (98 mg, 0,375 mmoles) se disolvieron en THF anhidro (1 mL) y seguido de la adición gota a gota de azodicarboxilato de dietilo (65 mg, 0,375 mmoles) en THF anhidro (1 mL) a temperatura ambiente mediante una jeringa. La solución de la reacción resultante se agitó a temperatura ambiente durante 18 horas y se concentró. La purificación mediante columna de gel de sílice con 20 – 40% de EtOAc en hexano produjo 69 mg (59%) de aceite amarillo claro.

^{1}H RMN ($CDCL_3$, 400 MHz): 1,55 (s, 6 H), 2,31 (s, 3 H), 3,10 (t, 2 H), 3,68 (s, 3 H), 4,25 (t, 2 H), 6,70 (m, 1 H), 6,82 (m, 1 H), 7,00 (s, 1 H), 7,05 (d, 1 H), 7,20 (m, 4 H), 7,32 (t, 2 H), 7,90 (d, 2 H)

EMBR: 472 $(M + H)^+$.

Ejemplo B – 1

Ácido (trifluorometil)fenil]etoxi}carbonilamino]metil}fenoxi)ciclobutanocarboxílico



A una solución de 1-(3-[[({2-[3-(trifluorometil)fenil]etoxi}carbonil)amino]metil}fenoxi)ciclobutanocarboxilato de etilo (0,150 g, 0,32 mmoles) en tetrahidrofurano (3 mL) y metanol (0,6 mL) a 0°C se añadió hidróxido de litio acuoso 2 M (0,32 mL, 2 equiv). La mezcla resultante se agitó a temperatura ambiente durante 24 horas. Se añadió agua (10 mL) y la mezcla se extrajo con éter dietílico (1 x 15 mL, desechado). Se ajustó la fase acuosa hasta pH 2 con ácido clorhídico 1 N y se extrajo con acetato de etilo (3 x 20 mL). Se lavaron los extractos orgánicos combinados con cloruro sódico acuoso saturado, se secaron (sulfato sódico anhidro), se filtraron y se concentraron hasta sequedad para producir el compuesto del título (85%).

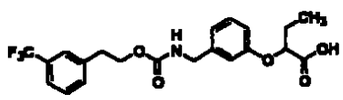
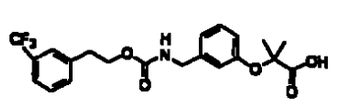
EMBR: 438 $(M + H)^+$.

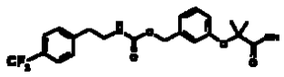
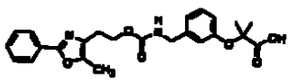
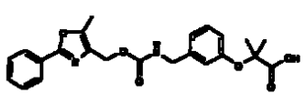
^{1}H RMN ($CDCL_3$, 400 MHz): 7,62 (1H, t, J = 7,8 Hz), 7,46 (1H, t, J = 7,3 Hz), 7,36 (1H, t, J = 7,3 Hz), 7,31 (1H, dd, J = 6,1, 7,6 Hz), 7,18 (1H, t, J = 8,0 Hz), 6,84 (1H, d, J = 7,6 Hz), 6,65 (1H, s), 6,56 (1H, d, J = 7,8 Hz), 4,32 – 4,27 (4H,

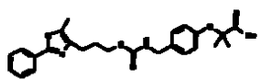
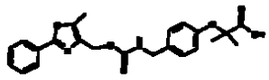
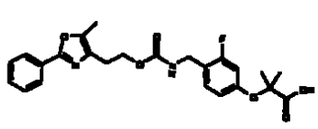
m), 3,11 (1H, t, *J* = 6,8 Hz), 2,79 – 2,72 (21H, m), 2,49 – 2,41 (2H, m), 2,09 – 1,93 (2H, m).

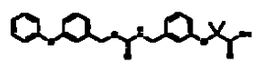
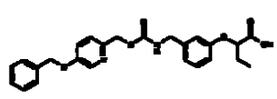
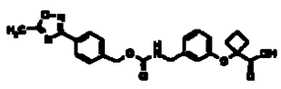
Ejemplo B – 2 a B – 29

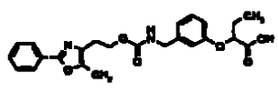
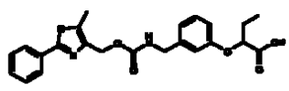
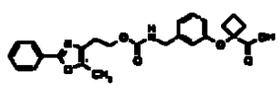
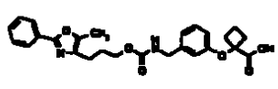
Los ejemplos B – 2 a B – 29 se prepararon mediante procedimientos análogos al usado para el ejemplo B – 1

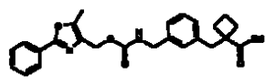
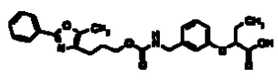
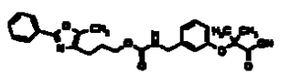
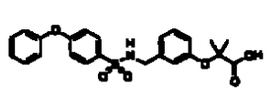
Ejemplo nº	Estructura	^{1}H RMN	EM (m/z) (BR o AR)
B – 2		^{1}H RMN ($CDCL_3$, 400 MHz): 7,62 (1H, t, *J* = 7,8 Hz), 7,46 (1H, t, *J* = 7,3 Hz), 7,36 (1H, d, *J* = 7,6 Hz), 7,31 (1H, t, *J* = 7,6 Hz), 7,22 (1H, t, *J* = 7,8 Hz), 6,88 (1H, d, *J* = 7,3 Hz), 6,83 (1H, s), 6,78 (1H, dd, *J* = 1,9, 8,2 Hz), 4,60 (1H, t, *J* = 5,8 Hz), 4,36 – 4,29 (4H, m), 3,11 (2H, t, *J* = 6,8 Hz), 2,03 – 1,97 (2H, m), 1,08 (3H, t, *J* = 7,5 Hz).	para BR 426 $(M+H)^+$.
B – 3		^{1}H RMN ($CDCL_3$, 400 MHz): 7,62 (1H, t, *J* = 7,8 Hz), 7,46 (1H, t, *J* = 7,5 Hz), 7,36 (1H,	para BR 426 $(M+H)^+$.

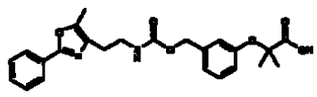
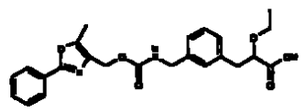
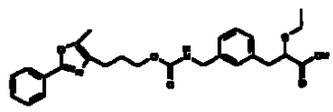
		d, J = 7,6 Hz), 7,31 (1H, t, J = 7,6 Hz), 7,21 (1H, t, J = 7,6 Hz), 6,94 (1H, d, J = 7,3 Hz), 6,86 (1H, s), 6,81(1H, d, J = 7,8 Hz), 4,36 – 4,29 (4H, m), 3,11 (2H, t, J = 7,0 Hz), 1,58 (6H, s).	
B – 4		^{1}H RMN ($CDCL_3$, 400 MHz): 1,69 (s, 6 H), 4,34 (d, 2 H), 5,05 – 5,17 (m, 1 H), 5,23 (s, 2 H), 6,71 (dd, 1 H), 6,78 (s, 1 H), 6,90 (d, 1 H), 7,18 – 7,23 (m, 1 H), 7,26 – 7,33 (m, 1 H), 7,69 (d, 1 H), 7,89 (d, 1 H), 8,73 (s, 1 H).	EMBR (*m/z*) 426,4 $(M+H)^+$.
B – 5		^{1}H RMN ($CDCL_3$, 400 MHz): 7,98 – 7,92 (2H, m), 7,44 – 7,38 (3H, m), 7,15 (1H, t, J = 7,7 Hz), 6,87 (1H, s), 6,84 – 6,79 (2H, m), 4,33 – 4,28 (4H, m), 2,89 (2H, t, J = 6,8 Hz), 2,32 (3H, s), 1,60 (6H, s).	para BR 439 $(M+H)^+$.
B – 6		^{1}H RMN ($CDCL_3$, 400 MHz): 1,58 (d, 6 H), 2,46 (s, 3 H), 4,32 (d, 2 H), 5,06 (s, 2 H), 6,70 – 6,72 (m, 1 H), 6,89 –	EMBR (*m/z*) 423,5 $(M+H)^+$.

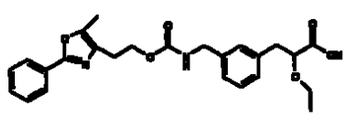
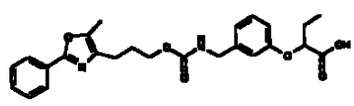
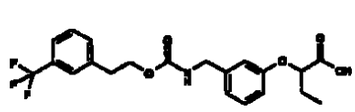
		6,91 (m, 1 H), 7,23 – 7,28 (m, 2 H), 7,39 – 7,48 (m, 2 H), 7,96 – 8,05 (m, 2 H).	
B – 7		^{1}H RMN ($CDCL_3$, 400 MHz): 1,63 (m, 6 H), 1,95 – 2,01 (m, 2 H), 2,34 (s, 3 H), 2,56 – 2,58 (m, 2 H), 4,11 – 4,13 (m, 2 H), 4,32 – 4,35 (d, 2 H), 4,89 – 4,92 (b, 1 H), 6,82 – 6,83 (m, 2 H), 7,21 – 7,27 (m, 3 H), 7,36 – 7,44 (m, 2 H), 7,93 – 7,96 (m, 2 H).	EMBR (*m/z*) 453,5 $(M+H)^+$.
B – 8		^{1}H RMN ($CDCL_3$, 400 MHz): 1,59 (s, 6 H), 2,47 (s, 3 H), 4,24 – 4,32 (m, 2 H), 4,99 – 5,09 (m, 3 H), 6,73 – 6,80 (m, 2 H), 7,15 (d, 2 H), 7,21 – 7,27 (m, 1 H), 7,37 – 7,46 (m, 2 H), 7,96 – 8,04 (m, 2 H).	EMBR (*m/z*) 425,5 $(M+H)^+$.
B – 9		^{1}H RMN ($CDCL_3$, 400 MHz): 1,64 (m, 6 H), 2,35 (s, 3 H), 2,82 (t, 2 H), 4,28 – 4,38 (m, 4 H), 6,55 (d, 2 H), 7,17 – 7,28 (m, 2 H), 7,36 – 7,45 (m, 2 H), 7,92 – 8,00 (m, 2 H).	EMBR (*m/z*) 457,5 $(M+H)^+$.

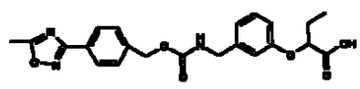
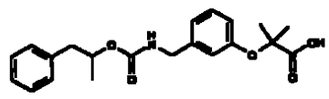
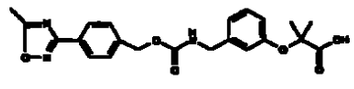
B – 10		^{1}H RMN ($CDCL_3$, 400 MHz): 1,67 (s, 6 H), 4,33 (d, 2 H), 5,03 – 5,14 (m, 3 H), 6,69 (dd, 1 H), 6,78 (s, 1 H), 6,92 (dd, 2 H), 7,01 (d, 3 H), 7,06 – 7,14 (m, 2 H), 7,18 (t, 1 H), 7,25 – 7,36 (m, 3 H).	EMBR (*m/z*) 435,5 $(M+H)^+$.
B – 11		^{1}H RMN ($CDCL_3$, 400 MHz): 1,05 – 1,16 (m, 3 H), 2,02 – 2,04 (m, 2 H), 4,11 – 4,13 (m, 1 H), 4,48 – 4,58 (m, 2 H), 4,95 – 5,96 (m, 1 H), 5,11 (s, 2 H), 5,21 (s, 2 H), 6,75 (d, 1 H), 6,83 – 6,93 (m, 2 H), 7,10 – 7,21 (m, 1 H), 7,30 – 7,41 (m, 6 H), 8,44 (s, 2 H).	EMBR (*m/z*) 451 $(M+H)^+$.
B – 12		^{1}H RMN ($CDCL_3$, 400 MHz): 8,06 – 8,00 (1H, m), 8,01 (1H, d, *J* = 7,6 Hz), 7,47 – 7,42 (1H, m), 7,43 (1H, d, *J* = 7,8 Hz), 7,19 (1H, t, *J* = 7,8 Hz), 6,87 (1H, d, *J* = 7,1 Hz), 6,68 (1H, s), 6,57 (1H, dd, *J* = 2,3, 8,1 Hz), 5,17 (2H, s), 4,32 (2H, d, *J* = 6,1 Hz), 2,80 – 2,75 (2H, m), 2,65 (3H, s),	para BR 426 $(M+H)^+$.

		2,49 – 2,41 (2H, m), 2,03 – 1,97 (2H, s).	
B – 13		^{1}H RMN ($CDCL_3$, 400 MHz): 0,85 – 0,95 (m, 3 H), 1,82 (s, 2 H), 2,13 (s, 3 H), 2,62 – 2,73 (m, 2 H), 3,85 (d, 1 H), 3,91 (s, 1 H), 4,30 – 4,41 (m, 2 H), 4,99 (s, 1 H), 6,58 (d, 1 H), 6,66 (s, 2 H), 6,94 – 7,06 (m, 2 H), 7,22 (s, 3 H), 7,70 – 7,81 (m, 2 H).	EMBR (*m/z*) 439 $(M+H)^+$.
B – 14		^{1}H RMN ($CDCL_3$, 400 MHz): 1,93 – 2,01 (m, 2 H), 2,46 (s, 3 H), 4,34 (d, 2 H), 4,56 – 4,57 (m, 1 H), 5,06 (s, 3 H), 6,74 – 6,76 (m, 1 H), 6,82 – 6,84 (m, 1 H), 6,89 – 6,91 (m, 1 H), 7,19 – 7,28 (m, 2 H), 7,41 – 7,46 (m, 2 H), 7,98 – 8,04 (m, 2 H).	EMBR (*m/z*) 425,5 $(M+H)^+$.
B – 15			para BR 415 $(M+H)^+$.
B – 16		^{1}H RMN ($CDCL_3$, 400 MHz): 7,96 – 7,94 (2H, m), 7,42 – 7,40 (3H, m), 7,19 (1H, t, *J* =	para BR 465 $(M+H)^+$.

		7,7 Hz), 6,79 (2H, t, J = 7,6 Hz), 6,60 (1H, s), 4,32 (1H, d, J = 6,1 Hz), 4,20 (2H, s), 2,81 – 2,75 (2H, m), 2,62 – 2,59 (1H, m), 2,49 – 2,41 (3H, m), 2,32 – 2,28 (2H, m), 2,08 (3H, s), 2,00 – 1,92 (3H, m).	
B - 17		^{1}H RMN ($CDCL_3$, 400 MHz): 1,94 – 2,05 (m, 2 H), 2,38 – 2,48 (m, 5 H), 2,68 – 2,76 (m, 2 H), 4,31 (d, 2 H), 5,06 (s, 3 H), 6,52 – 6,53 (m, 1 H), 6,65 – 6,67 (m, 1 H), 6,83 – 6,85 (m, 1 H), 7,16 – 7,17 (m, 1 H), 7,41 – 7,46 (m, 3 H), 7,99 – 8,03 (m, 2 H).	EMBR (*m/z*) 411,4 $(M+H)^+$.
B – 18			para BR 453 $(M+H)^+$.
B – 19			para BR 453 $(M+H)^+$.
B – 20		^{1}H RMN ($CDCL_3$, 400 MHz): 1,51 (s, 6 H), 4,02 (d, 2 H), 5,12 (s, 1 H), 6,72 – 6,80 (m, 2 H), 6,89 – 6,96 (m, 2 H),	EMBR (*m/z*) 442 $(M+H)^+$.

		6,96 – 7,02 (m, 2 H), 7,09 (t, 1 H), 7,29 (s, 2 H), 7,31 – 7,39 (m, 2 H), 7,64 – 7,73 (m, 2 H).	
B – 21		^{1}H RMN ($CDCL_3$, 400 MHz): 1,62 (s, 6 H), 2,30 (s, 3 H), 2,69 – 2,71 (m, 2 H), 3,49 – 3,58 (m, 2 H), 5,05 (s, 2 H), 5,36 – 5,38 (m, 1 H), 6,73 – 6,75 (m, 1 H), 6,97 – 6,99 (m, 1 H), 7,19 – 7,28 (m, 3 H), 7,38 – 7,48 (m, 1 H), 7,96 – 7,98 (m, 2 H).	EMBR (*m/z*) 439,5 $(M+H)^+$.
B – 22		^{1}H RMN ($CDCL_3$, 400 MHz): 1,19 – 1,26 (m, 3 H), 2,46 (s, 3 H), 2,93 – 3,02 (m, 2 H), 3,26 – 3,29 (m, 2 H), 3,99 – 4,01 (m, 1 H), 4,36 (d, 2 H), 5,06 (s, 3 H), 7,15 (m, 3 H), 7,40 – 7,47 (m, 3 H), 7,98 – 8,04 (m, 2 H).	EMBR (*m/z*) 439,5 $(M+H)^+$.
B – 23		^{1}H RMN ($CDCL_3$, 400 MHz): 1,21 – 1,27 (m, 3 H), 1,97 – 2,06 (m, 2 H), 2,34 (s, 3 H), 2,57 (t, 2 H), 2,95 – 3,03 (m, 2 H), 3,34 – 3,59 (m, 2 H), 4,11 – 4,20 (m, 4 H), 4,35 (d, 2 H),	EMBR (*m/z*) 467,5 $(M+H)^+$.

		4,96 – 4,98 (m, 1 H), 7,11 – 7,18 (m, 3 H), 7,21 – 7,27 (m, 3 H), 7,37 – 7,45 (m, 2 H), 7,93 – 7,99 (m 2 H).	
B – 24		^{1}H RMN ($CDCL_3$, 400 MHz): 1,26 – 1,28 (m, 3 H), 2,35 (s, 3 H), 2,86 – 2,88 (m, 2 H), 2,95 – 3,06 (m, 1 H), 3,47 – 3,52 (m, 2 H), 4,18 – 4,20 (m, 2 H), 4,29 – 4,40 (m, 4 H), 4,96 – 4,99 (m, 1 H), 7,10 – 7,18 (m, 2 H), 7,19 – 7,28 (m, 3 H), 7,35 – 7,46 (m, 2 H), 7,92 – 7,99 (m, 2 H).	EMBR (*m/z*) 453,5 $(M+H)^+$.
B – 25		^{1}H RMN ($CDCL_3$, 400 MHz): 1,07 (t, 3 H), 1,94 – 2,05 (m, 3 H), 2,17 (s, 3 H), 2,57 (t, 2 H), 4,15 (t, 1 H), 4,17 (d, 2 H), 4,33 (d, 2 H), 4,58 (m, 1 H), 6,83 (m, 1 H), 6,89 (m, 1 H), 6,95 (m, 1 H), 7,21 – 7,27 (m, 3 H), 7,37 – 7,44 (m, 2 H), 7,94 – 7,99 (m, 1 H).	EMBR (*m/z*) 453,5 $(M+H)^+$.
B – 26		^{1}H RMN ($CDCL_3$, 400 MHz): 1,65 (s, 6 H), 2,88 (d, 2 H), 3,46 (s, 2 H), 5,03 (d, 3 H),	EMBR (*m/z*) 426,4 $(M+H)^+$.

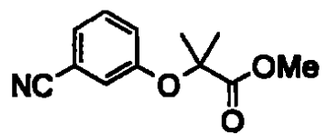
		6,73 (s, 1 H), 6,83 (d, 1 H), 6,89 – 7,00 (m, 1 H), 7,19 – 7,31 (m, 3 H), 7,55 (t, 2 H).	
B – 27		^{1}H RMN ($CDCL_3$, 400 MHz): 1,07 (t, 3 H), 1,98 (dc, 2 6 (s, 2 H), 4,57 – 4,59 (m, 1 H), (s, 2 H), 6,83 (m, 1 H), 6,89 (m, (t, 1 H), 7,48 (d, 2 H), 8,06 (d, 2 H).	EMBR (*m/z*) 426,5 $(M+H)^+$.
B – 28		^{1}H RMN ($CDCL_3$, 400 MHz): 1,21 (m, 3 H), 1,57 (s, 6 H), 2,63 – 2,84 (m, 2 H), 4,22 (d, 2 H), 4,83 – 4,85 (b, 1 H), 5,23 – 5,25 (m, 1 H), 6,84 – 6,87 (m, 3 H), 7,13 (dt, 2 H), 7,18 – 7,23 (m, 4 H).	EMBR (*m/z*) 372,4 $(M+H)^+$.
B – 29		^{1}H RMN ($CDCL_3$, 400 MHz): 1,78 (s, 6 H), 2,66 (s, 3 H), 4,34 (d, 2 H), 4,85 – 4,87 (b, 1 H), 5,05 – 5,06 (s, 2 H), 6,53 – 6,54 (m, 1 H), 6,67 – 6,69 (m, 1 H), 6,83 – 6,85 (m, 1 H), 7,13 (dt, 1 H), 7,18 – 7,23 (m, 2 H), 7,95 – 7,97 (m, 2 H).	EMBR (*m/z*) 426,5 $(M+H)^+$.

<u>Preparación de los materiales de partida para los ejemplos B- 1 a B – 29</u>

<u>(preparaciones b – 1 a b – 20)</u>

Preparación b – 1

2-(3-cianofenoxi)-2-metilpropanoato de metilo



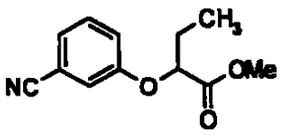
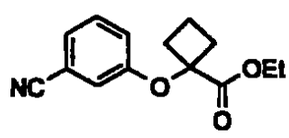
A una solución de 3-cianofenol (5 mmoles) en acetonitrilo (20 mL) o cualquier disolvente polar, aprótico tal como dimetilsulfóxido, *N,N*-dimetilformamida, etc) se añadió 2-bromo-2-metilpropanoato de metilo (1,2 equiv) y carbonato de cesio (2 equiv). La mezcla resultante se calentó a 60ºC durante 6 horas y después se enfrió hasta temperatura ambiente. Se introdujo agua (20 mL) y se extrajo la mezcla con acetato de etilo (3 x 20 mL). Los extractos orgánicos combinados se lavaron con bicarbonato sódico acuoso saturado y cloruro sódico acuoso saturado, se secaron (sulfato sódico anhidro), se filtraron, y se evaporaron hasta sequedad para proporcionar el compuesto del título con 75% de rendimiento.

EMBR: 220 $(M + H)^+$.

^1H RMN ($CDCL_3$, 400 MHz): 7,30 (1H, t, J = 8,0 Hz), 7,23 (1H, dt, J = 1,3, 7,6 Hz), 7,05 (1H, dd, J = 1,3, 2,3 Hz), 7,01 (1H, ddd, J = 2,3, 2,8, 8,3 Hz), 3,73 (3H, s), 1,57 (6H, s).

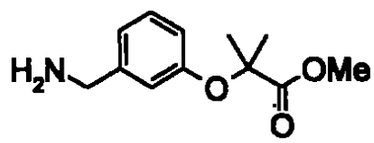
Preparación b – 2 a b – 3

Las preparaciones b – 2 a b – 3 se realizaron usando los procedimientos análogos a los descritos para la preparación b – 1

Preparación nº	Estructura	^{1}H RMN	EM (m/z) (BR o AR)
2		($CDCL_3$, 400 MHz): 7,33 (1H, dd, *J* = 7,6, 8,8 Hz), 7,22 (1H, dt, *J* = 1,3, 7,6 Hz), 7,09 – 7,06 (2H, m), 4,56 (1H, dd, *J* = 5,6, 6,6 Hz), 3,73 (3H, s), 2,01 – 1,93 (2H, m), 1,03 (3H, t, *J* = 7,5 Hz).	para BR 220 $(M+H)^+$.
3		($CDCL_3$, 400 MHz): 7,31 (1H, dd, *J* = 7,6, 9,1 Hz), 7,22 (1H, dt, *J* = 1,0, 7,8 Hz), 6,91 – 6,88 (2H, m), 4,20 (2H, c, *J* = 7,2 Hz), 2,78 – 2,71 (2H, m), 2,48 – 2,40 (2H, m), 2,08 – 1,96 (2H, m), 1,18 (3H, t, *J* = 7,2 Hz).	para BR 246 $(M+H)^+$.

Preparación b – 4

2-[3-(aminometil)fenoxi]-2-metilpropanoato de metilo



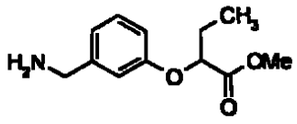
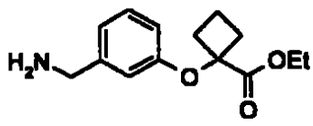
A una solución de 2-(3-cianofenoxi)-2-metilpropanoato de metilo (preparación b – 1) (4 mmoles) en metanol (20 mL) se añadió 10% de paladio sobre carbono (20% en peso). La mezcla resultante se agitó bajo a una atmósfera de nitrógeno durante 24 horas y se filtró a través de Celite. El filtrado se concentró y el residuo se puso en acetato de etilo y se lavó con ácido clorhídrico 1N (2 x 20 mL). Los lavados acuosos combinados se ajustaron hasta pH > 10 con hidróxido sódico acuoso 4 · N y se extrajeron con diclorometano (3 x 20 mL). Los extractos orgánicos combinados se lavaron con cloruro sódico acuoso saturado, se secaron (carbonato potásico), se filtraron y se concentraron hasta sequedad para proporcionar el compuesto del título con 65% de rendimiento.

EMBR: 224 $(M + H)^+$.

Preparación b – 5 a b – 6

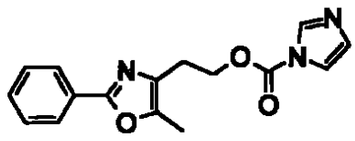
Las preparaciones b – 5 a b – 6 se realizaron usando los procedimientos análogos a los descritos para la preparación b – 4

Preparación nº	Estructura	^{1}H RMN	EM (m/z) (BR o AR)

b– 5		(CDCL$_3$, 400 MHz): 7,22 (1H, t, J = 7,8 Hz), 6,91 (1H, dt, J = 7,6 Hz), 6,86 (1H, s), 6,72 (1H, dd, J = 2,5, 8,1 Hz), 4,58 (1H, t, J = 6,2 Hz), 3,82 (2H, s), 3,74 (3H, s), 2,01 – 1,94 (2H, m), 1,06 (3H, t, J = 7,6 Hz).	para BR 224 $(M+H)^+$.
b– 6			para BR 250 $(M+H)^+$.

Preparación b – 7

1*H*-imidazol-1-carboxilato de 2-(5metil-2-fenil-1,3-oxazol-4-il)etilo



A una solución de 2-(5-metil-2-fenil-1,3-oxazol-4-il)etanol (1,015 g, 5 mmoles) en tolueno (25 mL) se añadió carbonato potásico (1,38 g, 2 equiv) y *N,N'*-carbonildiimidazol (0,97 g, 1,2 equiv). La mezcla resultante se agitó a

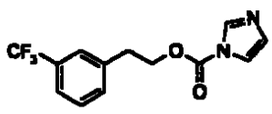
temperatura ambiente durante 24 horas antes de que se introdujera agua (20 mL). La extracción con acetato de etilo y el lavado de los extractos orgánicos combinados con cloruro sódico acuoso, el secado (sulfato sódico anhidro), la filtración y la concentración hasta sequedad produjo el compuesto del título (100%).

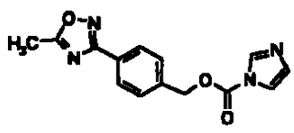
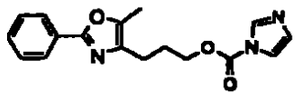
EMBR: 298 $(M + H)^+$.

^{1}H RMN ($CDCL_3$, 400 MHz): 8,10 (1H, s), 7,97 – 7,93 (2H, m), 7,44 – 7,39 (5H, m), 4,68 (2H, t, J = 6,7 Hz), 2,98 (2H, t, J = 6,7 Hz), 2,34 (3H, s).

Preparación b – 8 a b – 10

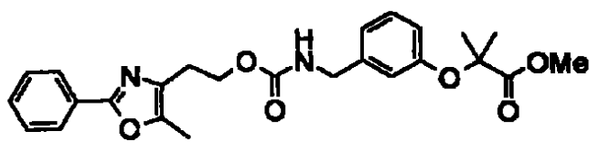
Las preparaciones b – 8 a b – 10 se realizaron usando los procedimientos análogos a los descritos para la preparación b – 7

Preparación nº	Estructura	^{1}H RMN	EM (m/z) (BR o AR)
b – 8		($CDCL_3$, 400 MHz): 8,10 (1H, s), 7,68 (1H, d, J = 7,6 Hz), 7,52 (1H, t, J = 7,6 Hz), 7,40 (1H, s), 7,38 (1H, s), 7,24 (1H, t, J = 7,3 Hz), 7,17 – 7,13 (1H, m), 4,63 (2H, t, J = 6,8 Hz), 3,29 (2H, t, J = 6,8 Hz).	para BR 285 $(M+H)^+$.

b – 9		(CDCL$_3$, 400 MHz): 8,49 (1H, s a), 8,13 (2H, d, *J* = 8,3 Hz), 7,57 (1H, s), 7,54 (2H, s), 7,26 – 7,24 (1H, m), 5,52 (2H, s), 2,66 (3H, s).	para BR 285 $(M+H)^+$.
b – 10			para BR 312 $(M+H)^+$.

Preparación b – 11

2-metil-2-{3-[({[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]carbonil}amino)metil]fenoxi}propanoato de metilo



A una solución de 1*H*-imidazol-1-carboxilato de 2-(5metil-2-fenil-1,3-oxazol-4-il)etilo (preparación 7) (0,48 g, 1,6 mmoles) en tetrahidrofurano (3 mL) se añadió 2-[3-(aminometil)fenoxi]-2-metilpropanoato de metilo (preparación b – 4) (0,39 g, 1,1 equiv). La mezcla resultante se calentó a reflujo durante 16 horas y después se enfrió hasta temperatura ambiente. La concentración y purificación mediante cromatografía sobre gel de sílice usando 0 – 50% de

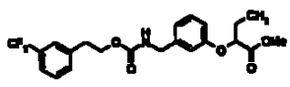
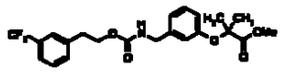
acetato de etilo en hexanos proporcionó el compuesto del título (0,39 g, 53%).

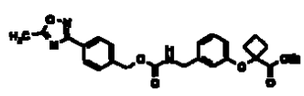
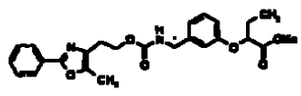
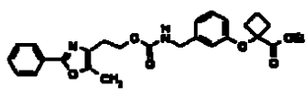
EMBR: 453 $(M + H)^+$.

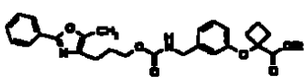
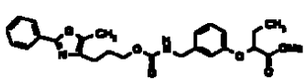
^{1}H RMN ($CDCL_3$, 400 MHz): 7,96 (2H, dd, J = 1,9, 7,7 Hz), 7,44 – 7,38 (3H, m), 7,16 (1H, t, J = 8,0 Hz), 6,89 (1H, dd, J = 7,3 Hz), 6,77 (1H, s), 6,67 (1H, dd, J = 2,3, 8,3 Hz), 4,36 (2H, dd, J = 6,7 Hz), 4,30 (2H, dd, J = 5,8 Hz), 3,75 (3H, s), 2,83 (2H, t, J = 6,7 Hz), 2,32 (3H, s), 1,57 (6H, s).

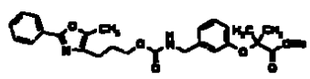
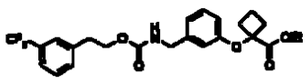
Preparación b – 12 a b – 20

Las preparaciones b – 12 a b – 20 se realizaron usando los procedimientos análogos a los descritos para la preparación b – 11

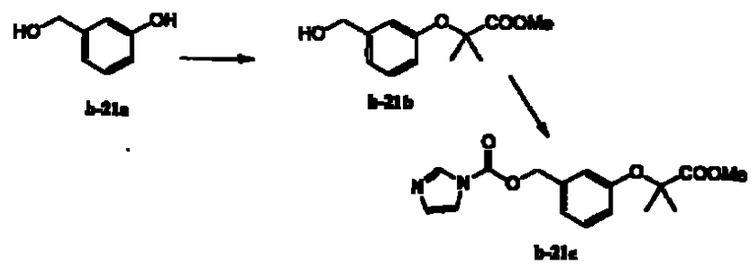
Preparación nº	Estructura	^{1}H RMN	EM (m/z) (BR o AR)
b– 12			para BR 440 $(M+H)^+$.
b– 13		($CDCL_3$, 400 MHz): 7,63 (1H, d, J = 7,8 Hz), 7,47 (1H, t, J = 7,5 Hz), 7,38 (1H, d, J = 6,3 Hz), 7,34 – 7,28 (1H, m), 7,18 (1H, dd, J = 7,6, 8,1 Hz), 6,89 (1H, d, J = 7,3 Hz), 6,77 (1H, s), 6,69 (1H, dd, J = 2,3, 8,3	para BR 440 $(M+H)^+$.

		Hz), 4,33 – 4,30 (4H, m), 3,75 (3H, s), 3,13 (2H, t, *J* = 7,0 Hz), 1,58 (6H, s).	
b– 14		($CDCL_3$, 400 MHz): 7,99 (2H, d, *J* = 8,1 Hz), 7,41 (2H, m), 7,11 (1H, t, *J* = 8,1 Hz), 6,79 (1H, d, *J* = 7,6 Hz), 6,60 (1H, s), 6,46 (1H, dd, *J* = 2,3, 8,1 Hz), 5,12 (2H, s), 4,27 (2H, d, *J* = 6,1 Hz), 4,12 (2H, c, *J* = 7,1 Hz), 2,71 – 2,60 (2H, m), 2,59 (3H, s), 2,42 – 2,32 (2H, m), 1,98 – 1,88 (2H, m), 1,09 (3H, t, *J* = 7,1 Hz).	para BR 440 $(M+H)^+$.
b– 15			para BR 453 $(M+H)^+$.
b– 16		($CDCL_3$, 400 MHz): 7,96 (2H, dd, *J* = 1,9, 7,7 Hz), 7,44 – 7,36 (3H, m), 7,18 – 7,13 (1H, m), 6,85 (1H, d, *J* = 7,6 Hz), 6,66 (1H, s), 6,50 (1H, dt, *J* = 1,3, 8,1 Hz), 4,35 (2H, t, *J* = 7,1 Hz), 4,29 (2H, d, *J* = 6,1 Hz), 4,11 (2H, c, *J* = 7,1 Hz), 2,83 (2H, t, *J* = 6,8 Hz), 2,77	para BR 479 $(M+H)^+$.

		– 2,69 (2H, m), 2,48 – 2,38 (2H, m), 2,32 (3H, s), 2,01 – 1,94 (2H, m), 1,16 (3H, t, *J* = 7,2 Hz).	
b– 17		($CDCL_3$, 400 MHz): 7,96 (2H, dd, *J* = 1,8, 7,8 Hz), 7,43 – 7,38 (3H, m), 7,17 (1H, t, *J* = 7,8 Hz), 6,85 (1H, d, *J* = 7,6 Hz), 6,66 (1H, s), 6,50 (1H, dd, *J* = 2,3, 8,1 Hz), 4,30 (2H, d, *J* = 5,8 Hz), 4,19 (2H, c, *J* = 7,3 Hz), 4,18 – 4,08 (2H, t, *J* = 7,5 Hz), 2,77 – 2,69 (2H, m), 2,56 (2H, t, *J* = 7,5 Hz), 2,48 – 2,39 (2H, m), 2,30 (3H, s), 2,02 – 1,94 (4H, m), 1,16 (3H, t, *J* = 7,1 Hz).	para BR 493 $(M+H)^+$.
b– 18		($CDCL_3$, 400 MHz): 7,96 (2H, dd, *J* = 1,8, 7,8 Hz), 7,43 – 7,38 (3H, m), 7,22 (1H, t, *J* = 8,1 Hz), 6,89 (1H, d, *J* = 7,8 Hz), 6,82 (1H, s), 6,74 (1H, dd, *J* = 2,2, 8,2 Hz), 4,56 (1H, t, *J* = 6,2 Hz), 4,32 (2H, d, *J* = 5,8 Hz), 4,14 (2H, t, *J* = 6,3 Hz), 3,74 (3H, s), 2,56 (2H, t, *J* = 7,3 Hz), 2,30 (3H, s), 2,03	para BR 467 $(M+H)^+$.

		– 1,93 (4H, m), 1,06 (3H, t, *J* = 7,3 Hz).	
b– 19		($CDCL_3$, 400 MHz): 7,96 (2H, dd, *J* = 1,8, 7,8 Hz), 7,43 – 7,38 (3H, m), 7,18 (1H, t, *J* = 8,0 Hz), 6,90 (1H, d, *J* = 7,6 Hz), 6,78 (1H, s), 6,68 (1H, dd, *J* = 2,2, 8,0 Hz), 4,31 (2H, d, *J* = 6,1 Hz), 4,13 (2H, t, *J* = 6,1 Hz), 3,75 (3H, s), 2,56 (2H, t, *J* = 7,3 Hz), 2,30 (3H, s), 2,00 (2H, t, *J* = 7,1 Hz), 1,58 (6H, s).	para BR 467 $(M+H)^+$.
b– 20		($CDCL_3$, 400 MHz): 7,63 (1H, d, *J* = 7,8 Hz), 7,47 (1H, t, *J* = 7,6 Hz), 7,38 (1H, d, *J* = 7,6 Hz), 7,32 (1H, d, *J* = 7,7 Hz), 7,16 (1H, d, *J* = 8,0 Hz), 6,83 (1H, d, *J* = 7,3 Hz), 6,65 (1H, s), 6,51 (1H, dd, *J* = 2,3, 8,1 Hz), 4,33 – 4,29 (4H, m), 4,18 (2H, c, *J* = 7,1 Hz), 3,13 (2H, t, *J* = 7,0 Hz), 2,76 – 2,69 (2H, m), 2,47 – 2,39 (2H, m), 2,01 – 1,94 (2H, m), 1,16 (3H, t, *J* = 7,1 Hz).	para BR 412 $(M+H)^+$.

Preparación b – 21



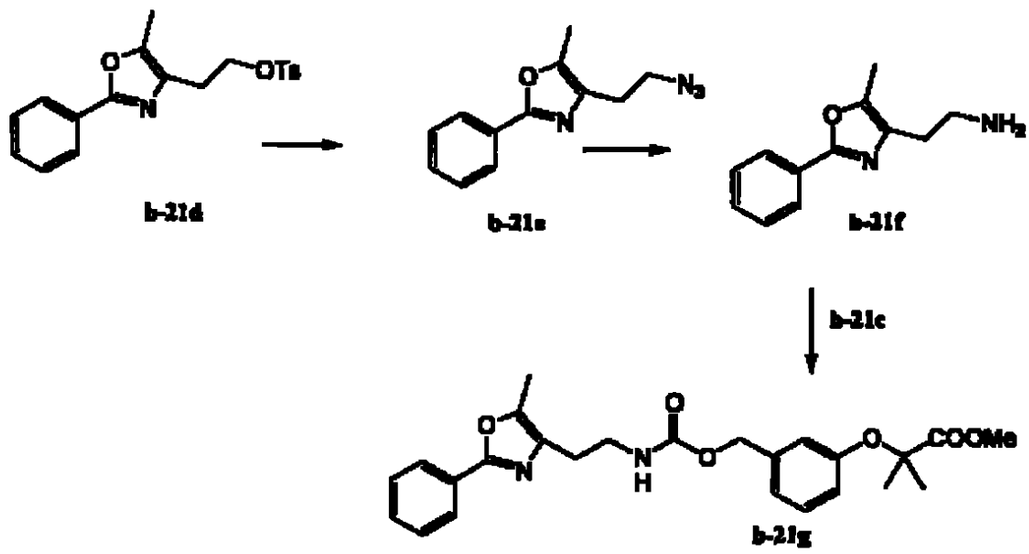
Preparación de imidazol b – 21c

A una solución del alcohol **b – 21c** (1 mmol) en tolueno (5 mL) se añadieron N, N"-carbonildiimidazol (1,05 mmoles) y carbonato potásico (1 mmol). La solución resultante se calentó a reflujo durante 3 horas. Después de enfriar hasta temperatura ambiente, se añadió agua (20 mL) y se extrajo la mezcla con acetato de etilo (3 x 20 mL). Se lavaron los extractos combinados con salmuera, se secaron sobre sulfato sódico y se concentraron a vacío para proporcionar el acilimidazol **b – 21c** con rendimiento cuantitativo.

Preparación de imidazol b – 21b

A una solución de alcohol 3-hidroxibencílico **b – 21a** (1 mmol) en carbonato de cesio (1 mL) en acetonitrilo (10 mL) se añadió 2-bromo-2-metilpropionato de metilo (2 mmoles). La mezcla se calentó a reflujo durante 6 horas. Después de enfriar hasta temperatura ambiente, se introdujo agua (50 mL) y la mezcla se extrajo con acetato de etilo (3 x 20 mL). Los extractos orgánicos combinados se lavaron con salmuera, se secaron sobre sulfato y se evaporaron a vacío. La cromatografía sobre gel de sílice (abreviadamente en inglés SGC) usando 10 – 30% de acetato de etilo – hexano proporcionó el

alcohol **b – 21b**. Los rendimientos variaban entre 40 – 85%.



Preparación del éster metílico **b – 21g**

Siguiendo los procedimientos descritos en b – 11, el éster metílico **b – 21g** se preparó haciendo reaccionar el compuesto **b – 21f** con el compuesto **b – 21c** con rendimientos que variaban entre 60 y 90%.

Preparación de la amina **b – 21f**

La solución de la azida **b – 21e** (2 mmoles) en acetato de etilo (20 mL) y paladio sobre carbono (10% en peso, 50 mg) se trató con hidrógeno gas a temperatura ambiente durante 4 horas. La eliminación de paladio mediante filtración a través de una almohadilla de Celite y concentración produjo la amina **b – 21f** con rendimiento cuantitativo.

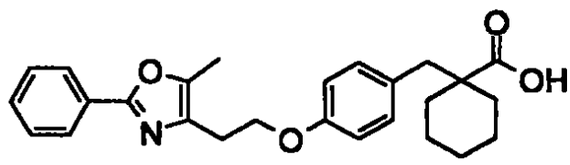
Preparación de la amina **b – 21e**

A una solución del tosilato **b – 21d** (1 mmoles) en DMF (5 mL) se añadió

azida sódica (3 mmoles). La mezcla resultante se agitó a temperatura ambiente durante 14 horas antes de que se añadiera agua (50 mL). La extracción con acetato de etilo (3 x 20 mL), lavado de los compuestos orgánicos combinados con agua, bicarbonato sódico saturado y salmuera, secado sobre sulfato sódico y concentración dio lugar a la azida **b – 21e** con 85% de rendimiento.

Ejemplo C – 1

Ácido 1-{4-[(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]bencil}ciclohexanocarboxílico



Se añadió trietilsilano (1,03 g, 8,86 mmoles) a una solución de 1-hidroxi{4-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]fenil}metil)ciclohexanocarboxilato de metilo (0,797 g, 1,77 mmoles) en diclorometano (5 mL) y ácido trifluoroacético (1 mL) a temperatura ambiente. Se agitó la mezcla resultante durante 1 hora después se evaporó a vacío y se destiló azeotrópicamente con heptano. Se disolvió el residuo en tetrahidrofurano (3 mL) y agua (3 mL) y se añadió hidróxido de litio monohidratado (0,223 g g, 5,31 mmoles). Se agitó la mezcla resultante a temperatura ambiente durante 18 horas, se acidificó hasta pH 2 con ácido clorhídrico 4 N y se extrajo con acetato de etilo. Se secó la fase orgánica (sulfato de magnesio anhidro), se filtró y se evaporó para producir el compuesto del título (0,332 g, 45%).

Análisis elemental: calculado para $C_{28}H_{29}NO_4$ C 74,44, H 6,97, N 3,34. Encontrado: C 74,22, H 6,89, N 3,34.

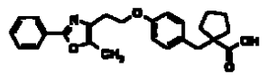
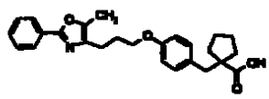
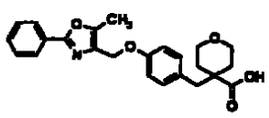
EMBR: 420 $(M + H)^+$.

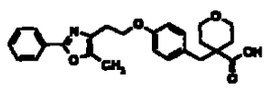
^{1}H RMN (DMSO-d_6, 400 MHz): 7,90 (2H, dd, J = 1,8, 7,8 Hz), 7,51 – 7,46 (3H, m), 6,98 (2H, d, J = 8,6 Hz), 6,80 (2H, d, J = 8,6 Hz), 4,16 (2H, t, J = 6,6 Hz), 2,90 (2H, d, J = 6,6 Hz), 2,64 (2H, s), 2,34 (3H, s), 1,85 (2H, d, J = 12,6, Hz), 1,53 – 1,46 (3H, m), 1,29 – 1,11 (5H, m).

Ejemplos C – 2 a C – 5

Los ejemplos C – 2 a C – 5 se prepararon mediante los procedimientos análogos a los usados para el ejemplo C – 1 con la excepción de que la etapa de la hidrólisis final se llevó a cabo disolviendo el residuo bruto en dimetilsulfóxido (75 mg/mL) e hidróxido sódico 6 N (1 mL) y calentando a 150°C durante 10 minutos en un sintetizador de microondas

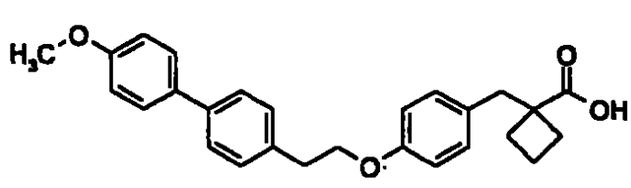
Ej. nº	Estructura	^{1}H RMN	EM (m/z) (BR o AR)	Análisis

C – 2		(DMSO-d_6, 400 MHz): 7,90 (2H, dd, *J* = 1,9, 7,7 Hz), 7,51 – 7,44 (3H, m), 7,04 (2H, d, *J* = 8,6 Hz), 6,80 (2H, d, *J* = 8,6 Hz), 4,15 (2H, t, *J* = 6,7 Hz), 2,9 (2H, t, *J* = 6,6 Hz), 2,79 (2H, s), 2,34 (3H, s), 2,05 – 2,00 (2H, m), 1,75 – 1,60 (6H, m).	para BR 406 $(M+H)^+$.	Calculado para $C_{25}H_{27}NO_4$ C 74,05, H 6,71, N 3,45. Encontrado: C 73,83, H 6,69, N 3,36
C – 3		(DMSO-d_6, 400 MHz): 7,89 (2H, dd, *J* = 1,8, 7,8 Hz), 7,51 – 7,46 (3H, m), 7,04 (2H, d, *J* = 8,6 Hz), 6,81 (2H, d, *J* = 8,6 Hz), 3,93 (2H, t, *J* = 6,2 Hz), 2,79 (2H, s), 2,60 (2H, t, *J* = 7,3 Hz), 2,27 (3H, s), 2,04 – 1,97 (2H, m), 1,92 – 1,85 (2H, m), 1,61 – 1,46 (6H, m).	para BR 420 $(M+H)^+$.	Calculado para $C_{26}H_{29}NO_4$ C 74,44, H 6,97, N 3,34. Encontrado: C 74,30, H 6,95, N 3,26
C – 4		(DMSO-d_6, 400 MHz): 7,94 – 7,92 (2H, m), 7,54 – 7,48 (3H, m), 7,04 (2H, d, *J* = 8,6 Hz), 6,92 (2H, d, *J* = 8,6 Hz), 4,95 (2H, s), 3,75 –	para BR 408 $(M+H)^+$.	Calculado para $C_{24}H_{25}NO_5$ C 70,75, H 6,18, N

		3,70 (2H, m), 3,28 (2H, dd, *J* = 10,0, 11,2 Hz), 2,73 (2H, s), 2,43 (3H, s), 1,81 (2H, d, *J* = 13,1 Hz), 1,49 – 1,42 (2H, m).		3,44. Encontrado: C 70,60, H 6,33, N 3,31
C – 5		(DMSO-d_6, 400 MHz): 7,90 (2H, dd, *J* = 1,9, 7,7 Hz), 7,51 – 7,44 (3H, m), 6,99 (2H, d, *J* = 8,6 Hz), 6,81 (2H, d, *J* = 8,6 Hz), 4,16 (2H, t, *J* = 6,6 Hz), 3,74 – 3,69 (2H, m), 3,27 (2H, t, *J* = 10,6 Hz), 2,90 (2H, t, *J* = 6,4 Hz), 2,71 (2H, s), 2,34 (3H, s), 1,79 (2H, d, *J* = 13,1 Hz), 1,47 – 1,39 (2H, m).	para BR 422 $(M+H)^+$.	Calculado para $C_{25}H_{27}NO_5$ C 71,24, H 6,46, N 3,32. Encontrado: C 71,01, H 6,47, N 3,32

Ejemplo C – 6

Ácido 1-[4-[2-(4'-metoxi-1,1'-bifenil-4-il)etoxi]bencil]ciclobutanocarboxílico



A una solución de 1-[4-[2-(4'-metoxi-1,1'-bifenil-4-

il)etoxi]bencil}ciclobutanocarboxilato de etilo (preparación 14) (0,3921 mmoles, 1 equiv.) en acetonitrilo (2 mL) se añadió hidróxido sódico acuoso 1 N (7,2 mL, 8 equiv.). Se sometió la mezcla resultante a calentamiento por microondas (100°C) en un sintetizador Personal Chemistry Smith durante 40 minutos. Después de enfriar la mezcla de reacción, se añadió ácido clorhídrico acuoso 1 M hasta que se logró pH 1. La mezcla se extrajo con acetato de etilo (3 x 50 mL). Después los extractos orgánicos combinados se lavaron con cloruro sódico acuoso saturado (100 mL), se secaron (sulfato magnésico anhidro), se filtraron y se concentraron a vacío para proporcionar el producto bruto. El residuo se purificó mediante trituración con éter dietílico para producir el compuesto del título en forma de un sólido blanco cristalino (0,1321 g, 81%).

Análisis elemental: calculado para $C_{27}H_{28}O_4$ C 77,86, H 6,78. Encontrado: C 77,65, N 6,85.

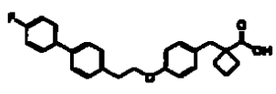
EMBR: *(m/z)* 416 $(M)^-$.

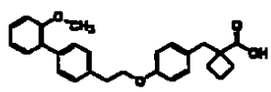
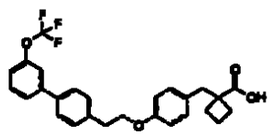
^{1}H RMN (acetona-d_6, 300 MHz): 7,53 (2H, d, *J* = 6,1 Hz), 7,66 (2H, d, *J* = 5,1 Hz), 7,46 (2H, d, *J* = 8,5 Hz), 7,13 (2H, d, *J* = 8,7 Hz), 7,07 (2H, d, *J* = 8,7 Hz), 6,85 (2H, d, *J* = 8,5 Hz), 4,20 (1H, t, *J* = 6,1 Hz), 3,86 (3H, s), 3,10 (2H, t, *J* = 7,0 Hz), 3,00 (2H, s), 2,40 – 2,30 (2H, m), 2,07 – 1,98 (2H, m), 1,92 – 1,80 (2H, m).

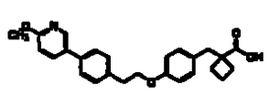
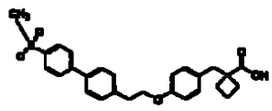
Ejemplos C – 7 a C – 93

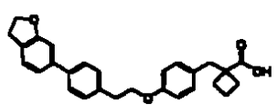
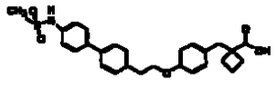
Los ejemplos C – 7 a C – 93 se prepararon mediante los procedimientos análogos a los usados para el ejemplo C – 6 o mediante la agitación de una solución del éster con hidróxido sódico o de litio en metanol acuoso, etanol acuoso, tetrahidrofurano acuoso o mezclas de los mismos a temperaturas entre

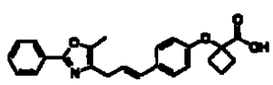
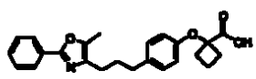
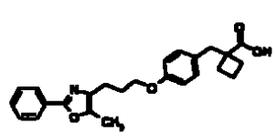
20°C y 75°C

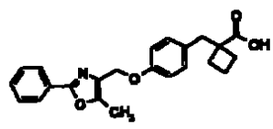
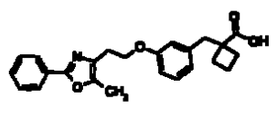
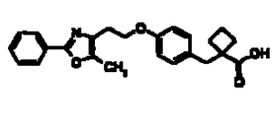
Ej. nº	Estructura	^{1}H RMN	EM (m/z) (BR o AR)	Análisis
C – 7		(Acetona-d_6, 300 MHz): 7,48 (2H, d, *J* = 8,9 Hz), 7,58 (2H, d, *J* = 8,7 Hz), 7,41 (2H, d, *J* = 8,5 Hz), 7,13 (2H, t, *J* = 8,9 Hz), 7,07 (2H, t, *J* = 8,7 Hz), 6,78 (2H, d, *J* = 8,7 Hz), 4,14 (2H, t, *J* = 7,0 Hz), 3,03 (2H, t, *J* = 7,0 Hz), 2,97 (2H, s), 2,40 – 2,30 (2H, m), 2,01 – 1,92 (2H, m), 1,85 – 1,72 (2H, m).	para BR 404 $(M+H)^-$.	Calculado para $C_{28}H_{25}FO_3$ C 77,21, H 6,23. Encontrado: C 77,13, H 6,28.

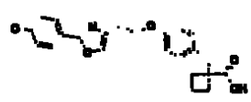
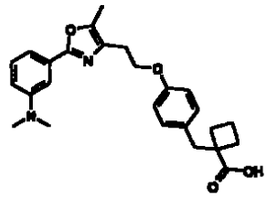
C – 8		(Acetona-d_6, 300 MHz): 7,58 (2H, d, *J* = 8,3 Hz), 7,41 (2H, d, *J* = 8,3 Hz), 7,34 (2H, t, *J* = 7,9 Hz), 7,21 – 7,15 (2H, m), 7,12 (2H, d, *J* = 8,7 Hz), 6,90 (1H, ddd, *J* = 0,94, 2,64, 8,3 Hz), 6,83 (2H, d, *J* = 8,7 Hz), 4,19 (2H, t, *J* = 6,9 Hz), 3,85 (3H, s), 3,09 (2H, t, *J* = 6,8 Hz), 3,02 (2H, s), 2,39 – 2,30 (2H, m), 2,07 – 1,98 (2H, m), 1,89 – 1,81 (2H, m).	para BR 416 $(M+H)^+$.	Calculado para $C_{27}H_{28}O_4C$ 77,86, H ·6,78. Encontrado: C 77,67, H 6,67.
C – 9		(Acetona-d_6, 300 MHz): 7,69 (1H, dt, *J* = 0,9, 8,3 Hz), 7,65 (2H, d, *J* = 8,3 Hz), 7,58 (2H, t, *J* = 8,1 Hz), 7,47 (2H, d, *J* = 8,3 Hz), 7,31 (1H, dt, *J* = 1,1, 8,1 Hz), 7,13 (2H, d, *J* = 8,7 Hz), 6,83 (2H, d, *J* = 8,7 Hz), 4,21 (2H, t, *J* = 6,8 Hz), 3,12 (2H, t, *J* = 6,8 Hz), 3,03 (2H, s), 2,40 – 2,30 (2H, m), 2,08 – 1,98 (2H, m), 1,92 – 1,79	para BR 470 $(M+H)^+$.	Calculado para $C_{27}H_{28}F_3O_4$ C 68,93, H 5,36. Encontrado: C 69,04, H 5,47.

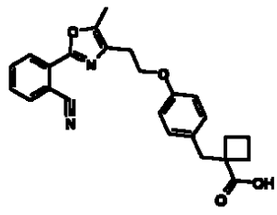
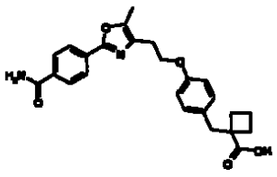
		(2H, m).		
C – 10		(Acetona-d_6, 300 MHz): 8,42 (1H, d, *J* = 2,6 Hz), 7,93 (1H, dd, *J* = 2,6, 8,7 Hz), 7,57 (2H, d, *J* = 8,3 Hz), 7,44 (2H, d, *J* = 8,3 Hz), 7,13 (2H, d, *J* = 8,9 Hz), 6,84 (2H, d, *J* = 8,7 Hz), 6,85 – 6,81 (1H, m), 4,20 (2H, t, *J* = 6,8 Hz), 3,91 (3H, s), 3,10 (2H, t, *J* = 7,0 Hz), 3,03 (2H, s), 2,40 – 2,30 (2H, m), 2,07 – 1,99 (2H, m), 1,90 – 1,82 (2H, m).	para BR 417 $(M+H)^+$.	Calculado para $C_{28}H_{27}NO_4$ C 74,80, H 6,52, H 3,35. Encontrado: C 74,67, H 6,46, N 3,31.
C – 11		(Acetona-d_6, 300 MHz): 8,01 (2H, d, *J* = 8,5 Hz), 7,92 (2H, d, *J* = 8,5 Hz), 7,70 (2H, d, *J* = 8,5 Hz), 7,50 (2H, d, *J* = 8,1 Hz), 7,13 (2H, d, *J* = 8,7 Hz), 6,84 (2H, d, *J* = 8,7 Hz), 4,22 (2H, t, *J* = 6,8 Hz), 3,15 (3H, s), 3,13 (2H, t, *J* = 6,8 Hz), 3,03 (2H, s), 2,40 – 2,30 (2H, m), 2,07 – 1,98 (2H, m), 1,92 –	para BR 482 $(M+H)^+$.	Calculado para $C_{27}H_{26}O_5S$ C 69,80, H 6,07. Encontrado: C 69,41, H 6,12.

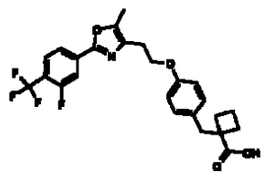
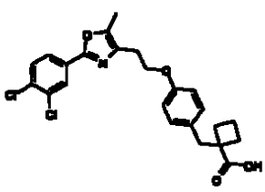
		1,79 (2H, m).		
C – 12		(Acetona-d_6, 300 MHz): 7,53 – 7,48 (1H, m), 7,52 (2H, d, *J* = 8,3 Hz), 7,38 – 7,34 (1H, m), 7,37 (2H, d, *J* = 8,3 Hz), 7,13 (2H, d, *J* = 8,7 Hz), 6,83 (2H, d, *J* = 8,7 Hz), 6,78 (1H, d, *J* = 8,3 Hz), 4,57 (2H, t, *J* = 8,7 Hz), 4,18 (2H, t, *J* = 6,8 Hz), 3,25 (2H, t, *J* = 8,7 Hz), 3,08 (2H, t, *J* = 7,0 Hz), 3,03 (2H, s), 2,40 – 2,30 (2H, m), 2,07 – 1,99 (2H, m), 1,92 – 1,79 (2H, m).	para BR 428 $(M+H)^-$.	Calculado para $C_{28}H_{28}O_4$ C 78,48, H 6,59. Encontrado: C 78,30, H 6,62.
C – 13		(Acetona-d_6, 300 MHz): 7,65 (2H, d, *J* = 8,7 Hz), 7,59 (2H, d, *J* = 8,1 Hz), 7,42 (4H, dd, *J* = 1,5, 8,1 Hz), 7,13 (2H, d, *J* = 8,5 Hz), 6,84 (2H, d, *J* = 8,9 Hz), 4,20 (2H, t, *J* = 6,8 Hz), 3,10 (2H, t, *J* = 6,8 Hz), 3,03 (2H, s), 3,01 (3H, s), 2,40 – 2,30 (2H, m), 2,07 – 1,99 (2H, m),	para BR 479 $(M+H)^-$.	Calculado para $C_{27}H_{29}NO_5S$ C 67,62, H 6,09, N 2,92. Encontrado: C 67,36, H 6,11, N 2,85.

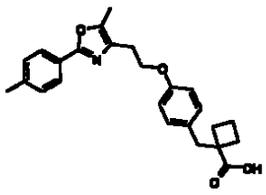
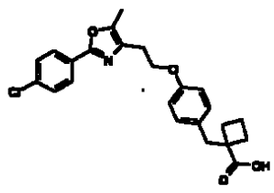
		1,92 – 1,81 (2H, m).		
C – 14		^{1}H RMN ($CDCl_3$, 400 MHz): 2,29 (s, 3 H), 2,39 (m, 2 H), 2,75 (m, 2 H), 3,00 (c, 2 H), 3,30 (d, 2 H), 6,00 (td, 1 H), 6,25 (d, 1 H), 6,56 (d, 2 H), 7,08 (d, 2 H), 7,35 (m, 3 H), 7,90 (m, 2 H).	EMBR *(m/z):* 390 $(M+H)^+$.	
C – 15		^{1}H RMN ($CDCl_3$, 400 MHz): 1,77, 1,89 (m, 2 H), 1,93 2,05 (m, 2 H), 2,27 (s, 3 H), 2,40 2,51 (m, 6 H), 2,71 2,80 (m, 2 H), 6,63 (d, 2 H), 6,97 (d, 2 H), 7,40 (dd, 3 H), 7,92 (m, 2 H).	EMBR *(m/z):* 392 $(M+H)^+$.	
C – 16		(DMSO-d_6, 400 MHz): 12,13 (1H, s), 7,86 (2H, m), 7,49 – 7.40 (3H, m), 7,01 (2H, d, *J* = 8,8 Hz), 6,78 (2H, t, *J* = 8,6 Hz), 3,90 (2H, t, *J* = 6,3 Hz), 2,89 (2H, s), 2,56 (2H, t, *J* = 7,3 Hz), 2,24 (3H, s), 2,24 – 2,15 (2H, m), 2,00	Calculado para $C_{25}H_{28}NO_4$ 406,2013 Encontrado: 406,2002	Calculado para $C_{25}H_{27}NO_4$ C 74,05, H 6,71, N 3,45. Encontrado: C 73,75, H 6,64, N

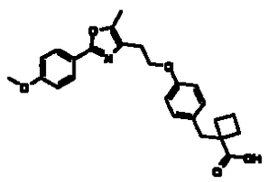
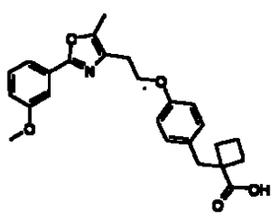
		– 1,67 (6H, m).		3,44
C – 17		(DMSO-d_6, 400 MHz): 12,04 (1H, s), 7,79 (2H, m), 7,40 – 7,34 (3H, m), 6,95 (2H, d, *J* = 8,6 Hz), 6,78 (2H, t, *J* = 8,6 Hz), 4,80 (2H, s), 2,80 (2H,s) 2,28 (3H, s), 2,12 – 2,06 (2H, m), 1,83 – 1,57 (4H, m).	Calculado para $C_{23}H_{24}NO_4$ 378,1700 Encontrado: 378,1692	Calculado para $C_{23}H_{23}NO_4$ C 73,19, H 6,14, N 3,71. Encontrado: C 73,15, H 6,26, N 3,75
C – 18		($CDCl_3$, 400 MHz): 8,00 – 7,97 (2H, m), 7,49 – 7,40 (3H, m), 7,17 (1H, d, *J* = 7,8 Hz), 7,03 (1H, s), 6,78 (2H, t, *J* = 7,1 Hz), 4,24 (2H, t, *J* = 8,1 Hz), 3,14 (2H, s), 2,90 (2H, t, *J* = 7,8 Hz), 2,51 – 2,40 (2H, m), 2,36 (3H, s), 2,07 – 1,83 (4H, m).	Calculado para $C_{24}H_{28}NO_4$ 392,1857 Encontrado: 392,1859	Calculado para $C_{24}H_{25}NO_4$ 0,2 H_2O C 72,96, H 6,48, N 3,55. Encontrado: C 72,66, H 6,65, N 3,47
C – 19		(DMSO-d_6, 400 MHz): 7,90 (2H, dd, *J* = 1,9, 7,7 Hz), 7,51 – 7,44 (3H, m), 7,05 (2H, d, *J* = 8,6 Hz),	para BR 392 $(M+H)^+$.	Calculado para $C_{24}H_{25}NO_4$ C 73,64, H

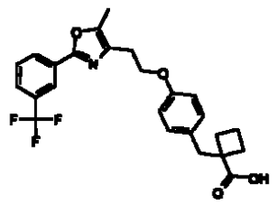
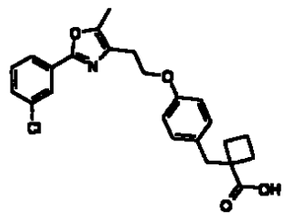
		6,81 (2H, d, J = 8,6 Hz), 4,15 (2H, t, J = 6,7 Hz), 2,92 (2H, s), 2,90 (2H, t, J = 6,8 Hz), 2,34 (3H, s), 2,25 – 2,18 (2H, m), 1,95 – 1,88 (2H, m), 1,86 – 1,71 (2H, m).		6,44, N 3,58. Encontrado: C 73,49, H 6,46, N 3,54
C – 20		^{1}H RMN (DMSO-d_6, 400 MHz): 7,83 (2H, d, J = 9,1 Hz), 7,06 – 7,02 (4H, m), 6,82 (2H, d, J = 8,6 Hz), 4,17 (2H, t, J = 6,3 Hz), 3,80 (3 H, s), 3,10 (2H, t, J = 6,3 Hz), 2,92 (2 H, s), 2,25 – 2,17 (2H, m) 2,08 (3 H, s), 1,95 – 1,69 (4 H, m).	Calculado para $C_{25}H_{28}NO_5$ 422,1962 Encontrado: 422,1961	
C – 21		(DMSO-d_6, 400 MHz): 7,25 – 7,24 (1H, m), 7,19 – 7,17 (2H, m), 7,00 – 6,97 (2H, m), 6,76 – 6,75 (1H, m), 6,72 – 6,70 (2H, m), 4,10 (2H, t, J = 6,5 Hz), 2,90 (6H, s), 2,85 (2H, t, J = 6,5 Hz), 2,25 (3H, s), 2,24 – 2,21 (2H, m), 1,95 – 1,92 (2H, m),	AR Calculado para $C_{28}H_{30}N_2O_4$ $(M+H)^+$. 435,2279 Encontrado:	

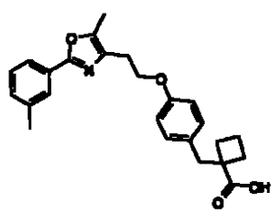
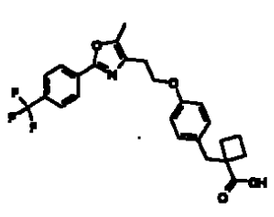
		1,78 – 1,74 (2H, m).	435,2270 para BR 435 $(M+H)^+$.	
C – 22		(CDCl$_3$, 400 MHz): 8,13 – 8,11 (2H, m), 7,77 – 7,75 (1H, m), 7,66 – 7,62 (1H, m), 7,49 – 7,45 (1H, m), 7,09 – 7,07 (2H, m), 6,81 – 6,79 (2H, m), 4,23 (2H, t, *J* = 6,3 Hz), 3,03 (2H, s), 2,99 (2H, t, *J* = 6,3 Hz), 2,46 – 2,38 (2H, m), 2,40 (3H, s), 2,09 – 2,02 (2H, m), 1,90 – 1,86 (2H, m).	AR Calculado para $C_{25}H_{24}N_2O_4$ $(M+H)^+$. 417,1809 Encontrado: 417,1813 para BR 418 $(M+H)^+$.	
C – 23		(DMSO-d$_6$, 400 MHz): 12,04 (1H, s), 7,89 – 7,84 (4H, m), 6,96 – 6,94 (2H, m), 6,72 – 6,70 (2H, m), 4,06 (2H, t, *J* = 6,5 Hz), 3,06 – 3,05 (1H, m), 2,82 – 2,80 (4H, m), 2,26 (3H, s), 2,15 – 2,08 (2H, m), 1,83 – 1,79 (2H, m), 1,69	AR Calculado para $C_{25}H_{28}N_2O_5$ $(M+H)^+$. 435,1915 Encontra	

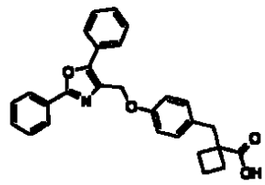
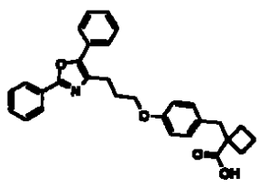
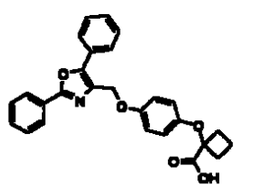
		– 1,65 (2H, m).	do: 435,1922 para BR 435 $(M+H)^+$.	
C – 24		($CDCl_3$, 400 MHz): 7,84 – 7,76 (2H, m), 7,66 – 7,61 (1H, m), 7,09 – 7,06 (2H, m), 6,80 – 6,77 (2H, m), 4,19 (2H, t, *J* = 6,5 Hz), 3,03 (2H, s), 2,96 (2H, t, *J* = 6,4 Hz), 2,47 – 2,40 (2H, m), 2,37 (3H, s), 2,10 – 2,01 (2H, m), 1,95 – 1,81 (2H, m).	AR Calculado para $C_{25}H_{23}NO_4F_4$ $(M+H)^+$. 478,1636 Encontrado: 478,1624 para BR 478 $(M+H)^+$.	
C – 25		($CDCl_3$, 400 MHz): 8,06 – 8,05 (1H, d), 7,80 – 7,77 (1H, m), 7,50 - 7,47 (1H, d), 7,09 – 7,06 (2H, m), 6,80 – 6,77 (2H, m), 4,19 (2H, t, *J* = 6,5 Hz), 3,03 (2H, s), 2,94 (2H, t, *J* = 6,5 Hz), 2,44 – 2,38 (2H,	AR Calculado para $C_{24}H_{23}NO_4Cl_2$ $(M+H)^+$. 460,1077 Encontra	

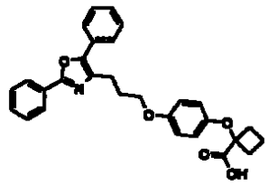
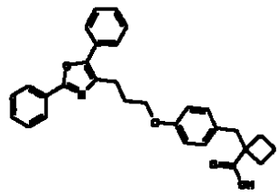
		m), 2,35 (3H, s), 2,08 – 2,01 (2H, m), 1,92 – 1,84 (2H, m).	do: 460,1089 para BR 461 $(M+H)^+$.	
C – 26		($CDCl_3$, 400 MHz): 7,87 – 7,85 (2H, m), 7,24 – 7,21 (2H, m), 7,09 – 7,07 (2H, m), 6,81 – 6,78 (2H, m), 4,20 – 4,17 (2H, m), 3,04 (2H, s), 2,98 – 2,94 (2H, m), 2,48 – 2,41 (2H, m), 2,38 (3H, s), 2,35 (3H, s), 2,10 – 2,02 (2H, m), 1,90 – 1,83 (2H, m).	AR Calculado para $C_{25}H_{27}NO_4$ $(M+H)^+$. 406,2013 Encontrado: 406,2014 para BR 406 $(M+H)^+$.	
C – 27		($CDCl_3$, 400 MHz): 7,91 – 7,88 (2H, m), 7,40 – 7,37 (2H, m), 7,09 – 7,06 (2H, m), 6,80 – 6,77 (2H, m), 4,18 (2H, t, J = 6,5 Hz), 3,03 (2H, s), 2,95 (2H, t, J = 6,5 Hz), 2,44 – 2,41 (2H, m), 2,35 (3H, s), 2,08	AR calculado para $C_{24}H_{24}NO_4Cl$ $(M+H)^+$. 426,1467 Encontra	

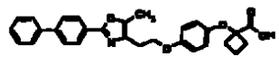
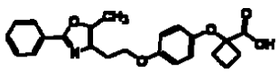
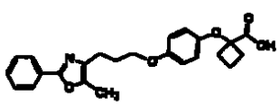
		– 2,01 (2H, m), 1,90 – 1,87 (2H, m).	do: 426,1471 Para BR 426 $(M+H)^+$.	
C – 28		($CDCl_3$, 400 MHz): 7,92 – 7,89 (2H, m), 7,10 – 7,07 (2H, m), 6,95 – 6,92 (2H, m), 6,80 – 6,77 (2H, m), 4,17 (2H, t, *J* = 6,5 Hz), 3,85 (3H, s), 3,04 (2H, s), 2,95 (2H, t, *J* = 6,5 Hz), 2,48 – 2,38 (2H, m), 2,34 (3H, s), 2,10 – 2,02 (2H, m), 1,94 – 1,83 (2H, m).	AR calculado para $C_{25}H_{27}NO_5$ $(M+H)^+$. 422,1962 Encontrado: 422,1948 Para BR 423 $(M+H)^+$.	
C – 29		($CDCl_3$, 400 MHz): 7,57 – 7,55 (1H, m), 7,51 – 7,49 (1H, m), 7,35 – 7,30 (1H, m), 7,10 – 7,07 (2H, m), 6,97 – 6,93 (1H, m), 6,81 – 6,78 (2H, m), 4,19 (2H, t, *J* = 6,5 Hz), 3,87 (3H, s), 3,04 (2H, s), 2,96 (2H, t, *J* = 6,5 Hz), 2,48 – 2,38	AR calculado para $C_{25}H_{27}NO_5$ $(M+H)^+$. 422,1962 Encontrado:	

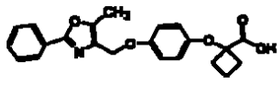
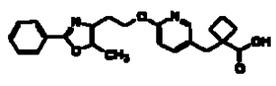
		(2H, m), 2,36 (3H, s), 2,11 – 2,02 (2H, m), 1,94 – 1,85 (2H, m).	422,1947 Para BR 422 $(M+H)^+$.	
C – 30		($CDCl_3$, 400 MHz): 8,23 (1H, s), 8,15 – 8,13 (1H, m), 7,64 – 7,63 (1H, m), 7,54 – 7,50 (1H, m), 7,07 – 7,05 (2H, m), 6,99 – 6,96 (1H, m), 6,77 – 6,75 (2H, m), 6,70 – 6,68 (1H, m), 4,19 (2H, t, *J* = 6,5 Hz).	AR calculado para $C_{25}H_{24}NO_4F_3$ $(M+H)^+$. 460,1730 Encontrado: 460,1728 Para BR 460 $(M+H)^+$.	
C – 31		($CDCl_3$, 400 MHz): 7,96 (1H, s), 7,86 – 7,83 (1H, m), 7,36 – 7,33 (2H, m), 7,09 – 7,06 (2H, m), 6,79 – 6,76 (2H, m), 4,18 (2H, t, *J* = 6,5 Hz), 3,03 (2H, s), 2,95 (2H, t, *J* = 6,5 Hz), 2,47 – 2,38 (2H, m), 2,35 (3H, s), 2,08 – 2,01 (2H, m), 1,91 – 1,84 (2H,	AR calculado para $C_{24}H_{24}NO_4Cl$ $(M+H)^+$. 426,1467 Encontrado: 426,1465	

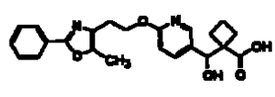
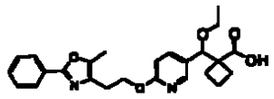
		m).	Para BR 426 $(M+H)^+$.	
C – 32		(CDCl$_3$, 400 MHz): 7,81 (1H, s), 7,77 – 7,75 (1H, m), 7,33 – 7,29 (1H, m), 7,22 – 7,20 (1H, m), 7,09 – 7,07 (2H, m), 6,81 – 6,78 (2H, m), 4,19 (2H, t, *J* = 6,5 Hz), 3,04 (2H, s), 2,96 (2H, t, *J* = 6,5 Hz), 2,44 – 2,42 (2H, m), 2,39 (3H, s), 2,35 (3H, s), 2,08 – 2,03 (2H, m), 1,89 – 1,87 (2H, m).	AR calculado para $C_{25}H_{27}NO_4$ $(M+H)^+$. 406,2013 Encontrado: 426,2026 Para BR 407 $(M+H)^+$.	
C – 33		(CDCl$_3$, 400 MHz): 8,08 – 8,06 (2H, d), 7,68 – 7,66 (2H, d), 7,09 – 7,07 (2H, m), 6,80 – 6,78 (2H, m), 4,91 (2H, t, *J* = 6,5 Hz), 3,03 (2H, s), 2,97 (2H, t, *J* = 6,5 Hz), 2,46 – 2,38 (2H, m), 2,37 (3H, s), 2,09 – 2,02 (2H, m), 1,92 – 1,82 (2H, m).	AR calculado para $C_{28}H_{24}NO_4F_3$ $(M+H)^+$. 460,1730 Encontrado: 460,1723 Para BR	

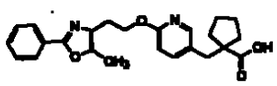
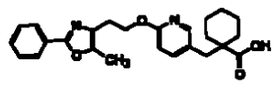
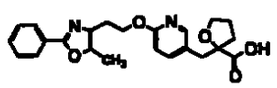
			461 $(M+H)^+$.	
C – 34		(DMSO-d_6, 300 MHz): 12,19 (1H, s), 8,12 – 8,11 (2H, m), 7,82 – 7,79 (2H, m), 7,59 – 7,44 (6H, m), 7,13 – 6,98 (4H, m), 5,17 (2H, s), 2,97 (2H, s), 2,30 – 2,21 (2H, m), 2,01 – 1,73 (4H, m).	calculado para $C_{28}H_{28}NO_4$ 440,1857 Encontrado: 440.1846	
C – 35		($CDCl_3$ 300 MHz): 8,09 – 8,07 (2H, m), 7,68 – 7,66 (2H, m), 7,46 – 7,26 (6H, m), 7,10 – 6,78 (4H, m), 4,01 (2H, t, *J* = 5,8 Hz), 3,04 – 3,00 (4H, m), 2,49 – 2,39 (2H, m), 2,30 – 2,21 (2H, m), 2,11 – 2,02 (2H, m), 1,94 – 1,81 (2H, m).	calculado para $C_{30}H_{30}NO_4$ 468,2107 Encontrado: 468,2165	
C – 36		(DMSO-d_6, 300 MHz): 12,92 (1H, s), 8,12 – 8,09 (2H, m), 7,82 – 7,79 (2H, m), 7,60 – 7,44 (6H, m), 7,02 – 6,99 (2H, m), 6,64 – 6,60 (2H, m), 5,13 (2H,	calculado para $C_{27}H_{24}NO_5$ 442,1649 Encontra	

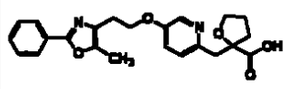
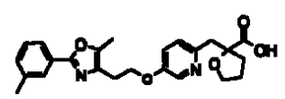
		s), 2,68 – 2,59 (2H, m), 2,37 – 2,26 (2H, m), 1,95 – 1,84 (2H, m).	do: 442,1639	
C – 37		($CDCl_3$, 300 MHz): 8,10 – 8,06 (2H, m), 7,69 – 7,66 (2H, m), 7,46 – 7,32 (6H, m), 6,79 – 6,66 (4H, m), 3,91 (2H, t, *J* = 6,0 Hz), 2,98 (2H, t, *J* = 7,3 Hz), 2,80 – 2,71 (2H, m), 2,50 – 2,40 (2H, m), 2,24 – 2,15 (2H, m), 2,06 – 1,93 (2H, m).	Calculado para $C_{29}H_{28}NO_4$ 470,1962 Encontrado: 470,1952	Calculado para $C_{29}H_{27}NO_5$ C 74,18, H 5,80, N 2,98. Encontrado: C 73,07, H 6,81, N 2,43
C – 38		($CDCl_3$, 300 MHz): 8,09 – 8,07 (2H, m), 7,68 – 7,66 (2H, m), 7,46 – 7,26 (6H, m), 7,10 – 6,78 (4H, m), 4,01 (2H, t, *J* = 5,8 Hz), 3,04 – 3,00 (4H, m), 2,49 – 2,39 (2H, m), 2,30 – 2,21 (2H, m), 2,11 – 2,02 (2H, m), 1,94 – 1,81 (2H, m).	Calculado para $C_{30}H_{28}NO_4$ $(M+H)^+$ 468,2107 Encontrado: 468,2165 para BR 468 $(M+H)^+$	

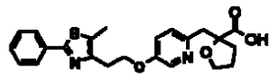
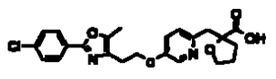
C – 39		($CDCl_3$, 400 MHz): 8,03 (2H, d, *J* = 8,3 Hz), 7,66 (2H, d, *J* = 8,3 Hz), 7,65 – 7,60 (2H, m), 7,49 – 7,32 (3H, m), 6,74 – 6,63 (4H, m), 4,03 (2H, t, *J* = 6,6 Hz), 2,96 (2H, t, *J* = 6,6 Hz), 2,81 – 2,70 (2H, m), 2,49 – 2,35 (2H, m), 2,38 (3H, s), 2,10 – 1,90 (2H, m).	Calculado para $C_{29}H_{29}NO_5$ 470,1962 Encontrado: 470,1948	Calculado para $C_{29}H_{27}NO_5$ C 74,18, H 5,80, N 2,98. Encontrado: C 74,07, H 5,83, N 2,89
C – 40		($CDCl_3$, 400 MHz): 8,00 – 7,93 (2H, m), 7,46 – 7,40 (3H, m), 6,73 – 6,62 (4H, m), 4,02 (2H, t, *J* = 6,6 Hz), 2,94 (2H, t, *J* = 6,6 Hz), 2,80 – 2,69 (2H, m), 2,47 – 2,33 (2H, m), 2,36 (3H, s), 2,10 – 1,88 (2H, m).	Calculado para $C_{23}H_{24}NO_5$ 394,1649 Encontrado: 394,1639	Calculado para $C_{23}H_{23}NO_5$ C 70,21, H 5,89, N 3,56. Encontrado: C 69,87, H 6,05, N 3,47
C – 41		($CDCl_3$, 400 MHz): 8,01 – 7,94 (2H, m), 7,47 – 7,39 (3H, m), 6,82 – 6,65 (4H, m), 3,87 (2H, d, *J* = 6,0 Hz), 2,82 – 2,71 (2H, m),	para BR 408 $(M+H)^+$	Calculado para $C_{24}H_{25}NO_5$ C 70,74, H 6,18, N

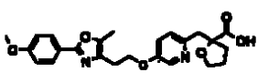
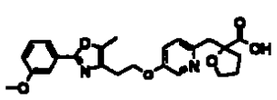
		2,67 – 2,60 (2H, m), 2,50 – 2,38 (2H, m), 2,29 (3H, s), 2,10 – 1,90 (4H, m).		3,44. Encontrado: C 70,52, H 6,19, N 3,41
C – 42		($CDCl_3$, 400 MHz): 8,04 – 7,97 (2H, m), 7,47 – 7,40 (3H, m), 6,86 – 6,63 (4H, m), 4,90 (2H, s), 2,78 – 2,70 (2H, m), 2,47 – 2,35 (2H, m), 2,41 (3H, s), 2,10 – 1,90 (2H, m).	para BR 380 $(M+H)^+$	Calculado para $C_{22}H_{21}NO_5$ C 69,64, H 5,58, N 6,69. Encontrado: C 69,49, H 5,68, N 3,62
C – 43		(MeOH-d_4, 400 MHz): 7,87 – 7,84 (3H, m), 7,46 (1H, dd, *J* = 2,3, 8,6 Hz), 7,39 – 7,35 (3H, m), 6,57 (1H, d, *J* = 8,6 Hz), 4,38 (2H, t, *J* = 6,7 Hz), 2,88 (4H, m), 2,25 (3H, s), 2,29 – 2,20 (2H, m), 1,88 – 1,81 (2H, m), 1,75 – 1,68 (2H, m).	Calculado para $C_{23}H_{24}N_2O_4$ 393,1809 Encontrado: 393,1815	

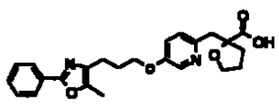
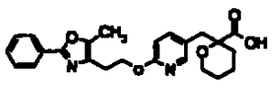
C – 44		(DMSO-d_6, 300 MHz): 8,02 (1H, d, *J* = 2,1 Hz), 7,91 – 7,88 (2H, m), 7,60 (1H, dd, *J* = 2,3, 8,5 Hz), 7,52 – 7,47 (3H, m), 6,72 (1H, d, *J* = 8,7 Hz), 5,66 (1H, s a), 4,73 (1H, s), 4,45 (2H, t, *J* = 6,8 Hz), 2,90 (2H, d, *J* = 6,7 Hz), 2,40 – 2,16 (2H, m), 2,30 (3H, m), 2,14 – 2,02 (2H, m), 1,75 – 1,63 (1H, m), 1,56 – 1,42 (1H, m).	para BR 408 $(M)^-$	Calculado para $C_{23}H_{24}N_2O_5$ C 67,63, H 5,92, N 6,86. Encontrado: C 67,51, H 6,08, N 6,75
C – 45		(Metilsulfóxido-d_6, 400 MHz): 8,02 (1H, d, *J* = 2,1 Hz), 7,91 – 7,88 (2H, m), 7,60 (1H, dd, *J* = 2,3, 8,5 Hz), 7,52 – 7,47 (3H, m), 6,72 (1H, d, *J* = 8,7 Hz), 4,68 (1H, s), 4,45 (2H, t, *J* = 6,8 Hz), 4,01 (2H, c, *J* = 7,1 Hz), 2,90 (2H, t, *J* = 6,7 Hz), 2,40 – 2,16 (2H, m), 2,30 (3H, s), 2,14 – 2,02 (2H, m), 1,75 – 1,63 (1H, m), 1,56 – 1,42 (1H, m), 1,29 (3H, t, *J* = 7,2	para BR 437 $(M+H)^+$	

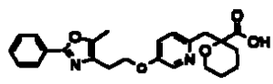
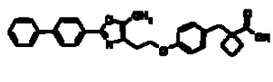
		Hz),.		
C – 46		($CDCl_3$, 400 MHz): 8,00 – 7,93 (3H, m), 7,42 – 7,37 (4H, m), 6,63 (1H, dd, *J* = 8,5 Hz), 4,48 (2H, t, *J* = 6,6 Hz), 2,96 (2H, t, *J* = 6,7 Hz), 2,86 (2H, s), 2,31 (3H, s), 2,10 – 2,02 (2H, m), 1,66 – 1,50 (6H, m).	para BR 406 $(M)^-$	
C – 47		($CDCl_3$, 400 MHz): 7,97 – 7,93 (3H, m), 7,43 – 7,33 (4H, m), 6,63 (1H, d, *J* = 8,5 Hz), 4,48 (2H, t, *J* = 6,8 Hz), 2,95 (2H, t, *J* = 6,8 Hz), 2,73 (2H, s), 2,30 (3H, s), 2,01 (2H, d, *J* = 12,6 Hz), 1,59 – 1,50 (3H, m), 1,40 – 1,15 (5H, m).	para BR 420 $(M)^-$	
C – 48		($CDCl_3$, 400 MHz): 7,99 – 7,94 (3H, m), 7,49 (1H, dd, *J* = 2,4, 8,6 Hz), 7,44 – 7,36 (3H, m), 6,63 (1H, d, *J* = 8,5 Hz), 4,50 (2H, t, *J* = 6,7 Hz), 4,00- 3,93	para BR 409 $(M)^+$	

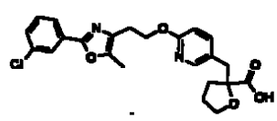
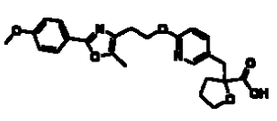
		(1H, m), 3,89 – 3,81 (1H, m), 3,14 (1H, d, *J* = 14,1 Hz), 2,95 (2H, t, *J* = 6,7 Hz), 2,85 (1H, d, *J* = 14,1 Hz), 2,31 (3H, s), 1,99 – 1,73 (4H, m).		
C – 49		(MeOH-d_4, 300 MHz): 8,37 (1H, d, *J* = 2,6 Hz), 8,07 (1H, dd, *J* = 2,6, 8,9 Hz),7,93 – 7,90 (2H, m), 7,79 (1H, d, *J* = 8,9 Hz), 7,47 – 7,40 (3H, m), 4,41 (2H, t, *J* = 6,2 Hz), 3,92 – 3,86 (2H, m), 3,05 (2H, t, *J* = 6,2 Hz), 2,36 (3H, s), 3,50 (1H, d, *J* = 14,3 Hz), 3,15 (1H, t, *J* = 14,3 Hz), 2,31 – 2,23 (1H, m), 2,00 – 1,92 (1H, m), 1,89 – 1,73 (2H, m).	para BR 408 $(M)^-$	Calculado para $C_{23}H_{25}N_2O_5$ Cl C 62,09, H 5,66, N 6,30. Encontrado: C 61,96, H 5,75, N 6,18
C – 50		(MeOD, 400 MHz): 8,37 (1H, d, *J* = 2,6 Hz), 8,07 (1H, dd, *J* = 2,6, 8,9 Hz), 7,93 – 7,90 (2H, m), 7,79 (1H, d, *J* = 8,9 Hz), 7,47 – 7,40 (2H, m), 4,41 (2H, t, *J* = 6,2 Hz), 3,92 – 3,86	para BR 423 $(M+H)^+$	

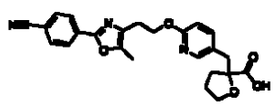
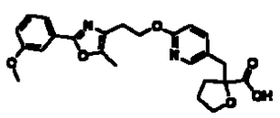
		(2H, m), 3,50 (1H, d, J = 14,3 Hz), 3,15 (1H, d, J = 14,3 Hz), 3,05 (2H, t, J = 6,2 Hz), 2,36 (3H, s), 2,34 (3H, m), 2,31 – 2,23 (1H, m), 2,00 – 1,92 (1H, m), 1,89 – 1,73 (2H, m).		
C – 51		($CDCl_3$, 400 MHz): 8,03 (1H, d, J = 2,5 Hz), 7,77 – 7,74 (2H, m), 7,36 – 7,31 (4H, m), 7,26 (1H, d, J = 8,6 Hz), 4,31 (2H, t, J = 6,6 Hz), 3,81 – 3,69 (2H, m), 3,11 (2H, t, J = 6,4 Hz), 3,02 (1H, d, J = 13,9 Hz), 2,37 (3H, s), 2,36 – 2,34 (1H, m), 2,18 – 2,11 (1H, m), 1,94 – 1,87 (1H, m), 1,78 – 1,68 (1H, m), 1,60 – 1,53 (1H, m).	para BR 425 $(M+H)^+$	
C – 52		($CDCl_3$, 400 MHz): 8,04 (1H, d, J = 2,8 Hz), 7,85 – 7,83 (2H, m), 7,41 – 7,39 (2H, m), 7,33 (1H, dd, J = 8,6, 3,0 Hz), 7,27 (1H, d, J = 8,8 Hz), 4,23 (2H, d, J = 6,3 Hz), 3,82 – 3,70 (2H,	para BR 443 $(M+H)^+$	

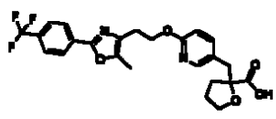
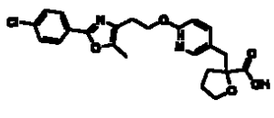
		m), 3,17 – 3,15 (1H, m), 3,03 (1H, d, *J* = 14,2 Hz), 2,91 (2H, d, *J* = 6,3 Hz), 2,29 (3H, s), 2,19 – 2,12 (1H, m), 1,96 – 1,88 (1H, m), 1,78 – 1,71 (1H, m), 1,61 – 1,54 (1H, m).		
C – 53		(MeOD, 400 MHz): 8,01 (1H, d, *J* = 1,5 Hz), 7,80 – 7,77 (2H, m), 7,25 – 7,24 (2H, m), 6,93 – 6,91 (2H, m), 4,20 (2H, d, *J* = 6,3 Hz), 3,80 – 3,69 (2H, m), 3,75 (3H, s), 3,17 – 3,15 (1H, m), 3,01 (1H, d, *J* = 13,9 Hz), 2,88 (2H, t, *J* = 6,3 Hz), 2,26 (3H, s), 2,17 – 2,11 (1H, m), 1,94 – 1,87 (1H, m), 1,75 – 1,66 (1H, m), 1,58 – 1,49 (1H, m).	para BR 439 $(M+H)^+$	
C – 54		(MeOD, 400 MHz): 8,01 (1H, d, *J* = 2,3 Hz), 7,44 – 7,40 (2H, m), 7,30 – 7,22 (3H, m), 6,94 – 6,91 (1H, m), 4,21 (2H, t, *J* = 6,4 Hz), 3,80 – 3,67 (2H, m),	para BR 439 $(M+H)^+$	

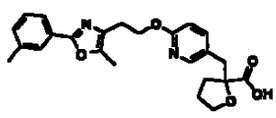
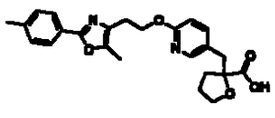
		3,75 (3H, s), 3,21 – 3,17 (1H, m), 3,01 (1H, d, *J* = 13,9 Hz), 2,90 (2H, t, *J* = 6,4 Hz), 2,28 (3H, s), 2,17 – 2,11 (1H, m), 1,94 – 1,87 (1H, m), 1,77 – 1,67 (1H, m), 1,60 – 1,50 (1H, m).		
C – 55		($CDCl_3$, 300 MHz): 8,43 (1H, d, *J* = 2,6 Hz), 7,97 – 7,93 (1H, m), 7,83 – 7,79 (1H, m), 7,60 – 7,52 (2H, m), 7,48 – 7,42 (3H, m), 4,14 (2H, t, *J* = 6,0 Hz), 4,06 – 3,99 (2H, m), 3,62 (1H, d, *J* = 13,9 Hz), 3,37 (1H, d, *J* = 13,9 Hz), 2,69 (2H, t, *J* = 6,0 Hz), 2,32 (3H, s), 2,23 – 1,96 (6H, m).	para BR 423 $(M+H)^+$	
C – 56		($CDCl_3$, 300 MHz): 7,93 – 8,03 (3H, m), 7,83 – 7,79 (1H, m), 7,37 – 7,54 (4H, m), 6,65 (1H, m), 4,50 (2H, t, *J* = 6,0 Hz), 3,75 (2H, m), 2,95 (4H, m), 2,33 (3H, s), 2,12 (2H,	para BR 423 $(M+H)^+$	

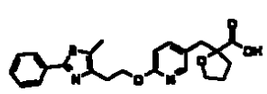
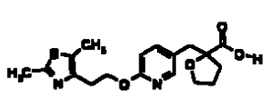
		m), 1,39 – 1,77 (5H, m).		
C – 57		(MeOD, 400 MHz): 7,98 (1H, d, *J* = 2,8 Hz), 7,86 – 7,84 (2H, m), 7,39 – 7,36 (3H, m), 7,24 (1H, d, *J* = 8,8, 2,8 Hz), 7,19 (1H, d, *J* = 8,6 Hz), 4,21 (2H, t, *J* = 6,6 Hz), 3,70 – 3,66 (1H, m), 3,60 – 3,53 (1H, m), 2,95 (2H, s), 2,90 (2H, t, *J* = 6,4 Hz), 2,28 (3H, s), 2,07 – 2,01 (1H, m), 1,61 – 1,58 (1H, m), 1,40 – 1,32 (4H, m).	para BR 423 $(M+H)^+$	
C – 58		(DMSO-d_6, 400 MHz): 8,17 (2H, d, *J* = 8,3 Hz), 7,99 (2H, d, *J* = 8,3 Hz), 7,92 (2H, d, *J* = 8,3 Hz), 7,68 (2H, t, *J* = 8,3 Hz), 7,58 (1H, t, *J* = 8,3 Hz), 7,24 – 7,02 (4H, m), 4,36 (2H, t, *J* = 6,6 Hz), 3,11 (2H, s), 3,11 – 3,07 (2H, m), 2,55 (3H, s), 2,44 – 2,37 (2H, m), 2,15 – 1,89 (4H, m).	Calculado para $C_{30}H_{30}NO_4$ 468,2170 Encontrado: 468,2163	Calculado para $C_{30}H_{30}NO_4.0,2H_2O$ C 76,47, H 6,29, N 2,97. Encontrado: C 76,48, H 6,30, N 2,90

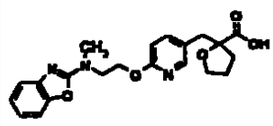
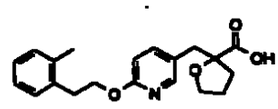
C – 59		^{1}H RMN (DMSO-d_6, 400 MHz): 8,04 (2H, d, *J* = 8,3 Hz), 7,95 – 7,93 (3H, m), 7,53 (1H, dd, *J* = 8,6 y 2,3 Hz), 6,69 (1H, d, *J* = 8,3 Hz), 4,45 (2H, t, *J* = 6,6 Hz), 3,75 (2H, t, *J* = 6,8 Hz), 3,01 (1H, d, *J* = 13,9 Hz), 2,93 (2H, t, *J* = 6,6 Hz), 2,82 (1H, d, *J* = 14,2 Hz), 2,33 (3H, s), 2,13 – 2,07 (1H, m), 1,84 – 1,62 (3H, m).		Calculado para $C_{23}H_{24}ClN_2O_5$ 443,1368 Encontrado: 443,1377
C – 60		^{1}H RMN (DMSO-d_6, 400 MHz): 12,45 (1H, s), 7,95 (1H, d, *J* = 2,3 Hz), 7,83 (2H, d, *J* = 8,8 Hz), 7,53 (1H, dd, *J* = 8,6 y 2,3 Hz), 7,03 (2H, d, *J* = 8,8 Hz), 6,69 (1H, d, *J* = 8,3 Hz), 4,42 (2H, t, *J* = 6,8 Hz), 3,80 (3H, s), 3,75 (2H, t, *J* = 6,8 Hz), 3,01 (1H, d, *J* = 13,9 Hz), 2,87 (2H, t, *J* = 6,8 Hz), 2,82 (1H, d, *J* = 14,2 Hz), 2,28 (3H, s), 2,14 – 2,07 (1H, m), 1,83		Calculado para $C_{24}H_{27}N_2O_6$ 439,1864 Encontrado: 439,1874

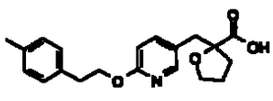
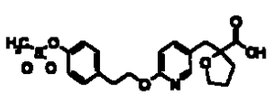
		– 1,63 (3H, m).		
C – 61		^{1}H RMN (DMSO-d_6, 400 MHz): 8,04 (2H, d, *J* = 8,3 Hz), 7,95 – 7,93 (3H, m), 7,53 (1H, dd, *J* = 8,6 y 2,3 Hz), 6,69 (1H, d, *J* = 8,3 Hz), 4,45 (2H, t, *J* = 6,6 Hz), 3,75 (2H, t, *J* = 6,8 Hz), 3,01 (1H, d, *J* = 13,9 Hz), 2,93 (2H, t, *J* = 6,6 Hz), 2,82 (1H, d, *J* = 14,2 Hz), 2,33 (3H, s), 2,13 – 2,07 (1H, m), 1,84 – 1,62 (3H, m).		Calculado para $C_{24}H_{24}N_3O_5$ 434,1711 Encontrado: 434,1705
C – 62		^{1}H RMN (DMSO-d_6, 400 MHz): 7,95 (1H, d, *J* = 2,0 Hz), 7,53 (1H, dd, *J* = 8,3 y 2,3 Hz), 7,48 (1H, d, *J* = 7,8 Hz), 7,42 – 7,38 (2H, m), 7,04 (1H, dd, *J* = 8,3 y 2,5 Hz), 6,69 (1H, d, *J* = 8,3 Hz), 4,43 (2H, t, *J* = 6,6 Hz), 3,81 (3H, s), 3,75 (2H, t, *J* = 6,8 Hz), 3,01 (1H, d, *J* = 13,9 Hz), 2,90 (2H, t, *J* = 6,6 Hz), 2,82 (1H, d, *J* = 13,9 Hz), 2,31		Calculado para $C_{24}H_{27}N_2O_6$ 439,1864 Encontrado: 439,1874

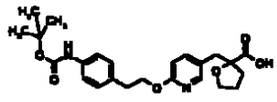
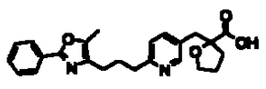
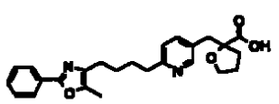
		(3H, s), 2,13 – 2,07 (1H, m), 1,83 – 1,58 (3H, m).		
C – 63		^{1}H RMN (DMSO-d_6, 400 MHz): 12,51 (1H, s), 8,10 (2H, d, *J* = 8,1 Hz), 7,95 (1H, d, *J* = 2,0 Hz), 7,85 (2H, d, *J* = 8,3 Hz), 7,53 (1H, dd, *J* = 8,3 y 2,3 Hz), 6,69 (1H, d, *J* = 8,6 Hz), 4,45 (2H, t, *J* = 6,8 Hz), 3,75 (2H, t, *J* = 6,6 Hz), 3,01 (1H, d, *J* = 13,9 Hz), 2,93 (2H, t, *J* = 6,6 Hz), 2,82 (1H, d, *J* = 13,9 Hz), 2,34 (3H, s), 2,13 – 2,06 (1H, m), 1,84 – 1,60 (3H, m).	Calculado para $C_{24}H_{24}F_3N_2O_6$ 477,1632 Encontrado: 477,1635	
C – 64		^{1}H RMN ($CDCl_3$, 400 MHz): 8,16 (1H, s), 7,88 (2H, d, *J* = 8,6 Hz), 7,81 (1H, d, *J* = 8,6 Hz), 7,41 (2H, d, *J* = 8,6 Hz), 6,87 (1H, d, *J* = 8,8 Hz), 4,51 (2H, t, *J* = 6,1 Hz), 4,03 – 3,90 (2H, m), 3,23 (1H, d, *J* = 14,2 Hz), 3,04 (2H, d, *J* = 6,1 Hz), 2,86 (1H, d, *J*	para BR 443 $(M+H)^+$	

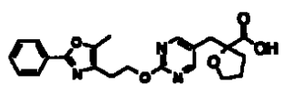
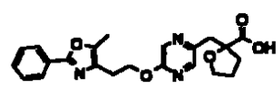
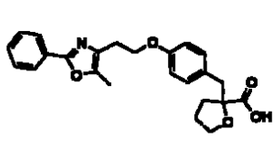
		= 14,2 Hz), 2,42 – 2,35 (1H, m), 2,37 (3H, s), 2,01 – 1,87 (3H, m).		
C – 65		^{1}H RMN (DMSO-d_6, 400 MHz): 7,95 (1H, d, *J* = 2,0 Hz), 7,73 (1H, s), 7,69 (1H, d, *J* = 7,3 Hz), 7,51 (1H, dd, *J* = 8,6 y 2,3 Hz), 7,37 (1H, t, *J* = 7,8 Hz), 7,28 (1H, d, *J* = 7,1 Hz), 6,69 (1H, d, *J* = 8,3 Hz), 4,43 (2H, t, *J* = 6,8 Hz), 3,75 (2H, t, *J* = 6,6 Hz), 3,01 (1H, d, *J* = 14,2 Hz), 2,89 (2H, t, *J* = 6,8 Hz), 2,82 (1H, d, *J* = 14,2 Hz), 2,36 (3H, s), 2,30 (3H, s), 2,14 – 2,08 (1H, m), 1,84 – 1,60 (3H, m).	Calculado para $C_{24}H_{27}N_2O_5$ 423,1915 Encontrado: 423,1927	Calculado para $C_{24}H_{28}N_2O_5.0,4H_2O$ C 64,23, H 6,01, N 6,19. Encontrado: C 64,16, H 6,16, N 6,01
C – 66		^{1}H RMN (DMSO-d_6, 400 MHz): 7,95 (1H, d, *J* = 2,3 Hz), 7,79 (2H, d, *J* = 8,1 Hz), 7,53 (1H, dd, *J* = 8,3 y 2,5 Hz), 7,29 (2H, d, *J* = 8,1 Hz), 6,68 (1H, d, *J* = 8,3 Hz), 4,43 (2H, t, *J* = 7,1 Hz), 3,75 (2H, t, *J* =	Calculado para $C_{24}H_{27}N_2O_5$ 423,1915 Encontrado: 423,1929	Calculado para $C_{24}H_{24}N_2O_5.0,9H_2O$ C 65,71, H 6,39, N 6,39. Encontrado:

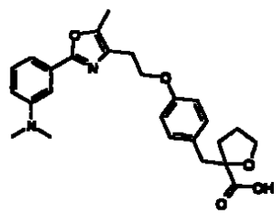
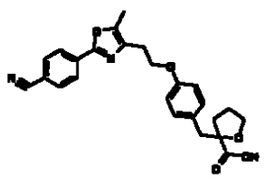
		6,8 Hz), 3,01 (1H, d, *J* = 13,9 Hz), 2,88 (2H, t, *J* = 6,8 Hz), 2,82 (1H, d, *J* = 13,9 Hz), 2,34 (3H, s), 2,29 (3H, s), 2,14 – 2,07 (1H, m), 1,84 – 1,60 (3H, m).		C 65,61, H 6,34, N 6,20
C – 67		^{1}H RMN (MeOH-d_4, 400 MHz): 8,28 (1 H, s), 7,76 (2 H, dt, *J* = 7,7, 0,2 Hz), 7,56 (1 H, d, *J* = 9,1 Hz), 7,34 – 7,39 (1 H, m), 7,14 – 7,20 (2 H, m), 6,28 (1H, d, *J* = 9,2 Hz), 4,12 (2 H, t, *J* = 8,0 Hz), 3,70 – 3,84 (2 H, m), 3,14 – 3,20 (1 H, m), 3,00 – 3,06 (1 H, m), 2,75 (2 H, d, *J* = 8,0 Hz), 2,34 – 2,44 (1 H, m), 2,26 – 2,31 (3 H, m), 1,82 – 2,05 (3H, m).	EMBR 426 $(M+H)^+$	
C – 68		^{1}H RMN (MeOH-d_4, 400 MHz): 8,28 (1 H, s), 7,56 (1 H, d, *J* = 9,1 Hz), 6,28 (1 H, d, *J* = 9,2 Hz), 4,12 (2H, t, *J* = 8,0 Hz), 3,70 – 3,84 (2 H, m), 3,14 – 3,20	para BR 364 $(M+H)^+$	

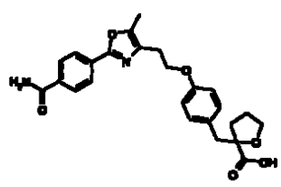
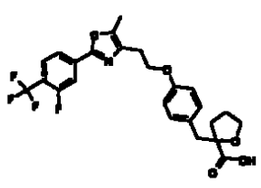
		(1 H, m), 2,99 – 3,06 (1 H, m), 2,58 (2 H, t, *J* = 8,0 Hz), 2,48 (3 H, s), 2,31 – 2,44 (1 H, m), 2,18 (3 H, s), 1,81 – 2,05 (3 H, m).		
C – 69		^{1}H RMN (MeOH-d_4, 400 MHz): 8,19 (1 H, s), 7,45 (2 H, dd, *J* = 9,0, 8,4 Hz), 7,33 (1 H, d, *J* = 7,7 Hz), 7,15 – 7,21 (1H, m), 6,99 – 7,05 (1 H, m), 6,24 (1 H, t, *J* = 9,2 Hz), 4,02 (2 H, t, *J* = 5,2 Hz), 3,70 – 3,84 (2 H, m), 3,42 (2 H, t, *J* = 5,2 Hz), 3,14 – 3,20 (1 H, m), 2,99 – 3,06 (1 H, m), 2,93 (3 H, s), 2,34 – 2,43 (1 H, m), 1,82 – 2,05 (3 H, m).	para BR 398 $(M+H)^+$	
C – 70		^{1}H RMN (MeOH-d_4, 400 MHz): 8,28 (1 H, s), 7,56 (1 H, d, *J* = 9,1 Hz), 7,08 – 7,20 (4 H, m), 6,28 (1 H, d, *J* = 9,2 Hz), 4,50 (2 H, t, *J* = 6,9 Hz), 3,70 – 3,84 (2 H, m), 3,14 – 3,20 (1 H, m), 3,00 – 3,05 (1 H,	para BR 342 $(M+H)^+$	

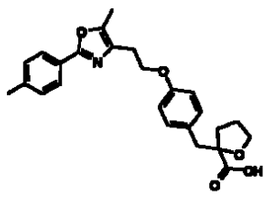
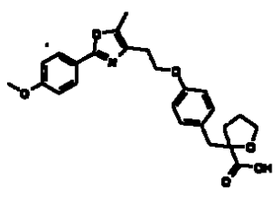
		m), 2,90 (2 H, t, *J* = 6,9 Hz), 2,32 – 2,43 (1 H, m), 2,28 (3 H, s), 1,81 – 2,05 (3 H, m).		
C – 71		^{1}H RMN (MeOH-d_4, 400 MHz): 8,28 (1 H, s), 7,56 (1 H, d, *J* = 9,1 Hz), 7,09 – 7,15 (4 H, m), 6,28 (1 H, d, *J* = 9,2 Hz), 4,57 (2 H, t, *J* = 6,5 Hz), 3,70 – 3,84 (2 H, m), 3,28 (2 H, d, *J* = 6,5 Hz), 3,14 – 3,20 (1 H, m), 3,00 – 3,06 (1 H, m), 2,34 – 2,44 (1 H, m), 2,27 – 2,31 (3H, m), 1,82 – 2,05 (3 H, m).	para BR 342 $(M+H)^+$	
C – 72		^{1}H RMN ($CDCl_3$, 400 MHz): 8,2 – 8,6 (1 H, s a), 8,10 (1 H, s), 7,58 (1 H, d, *J* = 9,1 Hz), 6,85 – 7,25 (4 H, m), 6,70 (1 H, d, *J* = 9,2 Hz), 3,80 – 4,05 (2 H, m), 3,63 (2 H, t, *J* = 6,5 Hz), 3,35 (3 H, s), 2,85 (2 H, t, *J* = 6,5 Hz), 2,30 (1 H, m), 1,65 – 2,05 (3 H, m).		

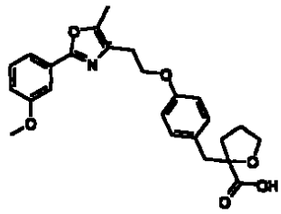
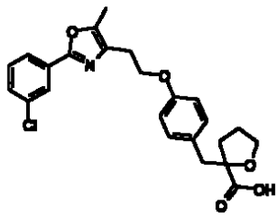
C – 73		^{1}H RMN ($CDCl_3$, 400 MHz): 7,98 (1 H, s), 7,48 (1 H, d, *J* = 9,1 Hz), 7,15 – 7,30 (4 H, m), 6,65 (2H, m), 4,37 (2 H, t, *J* = 6,5 Hz), 3,80 – 4,03 (2 H, m), 2,60 – 3,20 (4 H, m), 2,35 (3 H, m), 1,70 – 2,05 (3 H, m), 1,50 (9H, s).		
C – 74		(Acetona-d_6, 300 MHz): 8,37 (1 H, d, *J* = 1,9 Hz), 7,96 (2 H, m), 7,56 (1 H, dd, *J* = 7,9, 2,3 Hz), 7,45 (3 H, m), 7,14 (1 H, t, *J* = 7,9 Hz), 3,89 (2 H, m), 3,05 (2 H, m), 2,77 (2 H, m), 2,50 (2 H, t, *J* = 7,4 Hz), 2,30 (3 H, s), 2,16 (2 H, m), 1,88 (4 H, m).	para BR 405 $(M)^-$	
C – 75		(MeOD, 400 MHz): 8,19 (1 H, s), 7,82 – 7,80 (2 H, m), 7,61 (1 H, dd, *J* = 7,8, 1,8 Hz), 7,35 – 7,33 (3 H, m), 7,15 (1 H, d, *J* = 8,1 Hz), 3,83 – 3,73 (2 H, m), 3,09 (1 H, d, *J* = 13,9 Hz),	para BR 421 $(M+H)^+$	

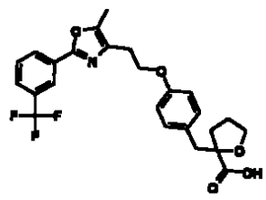
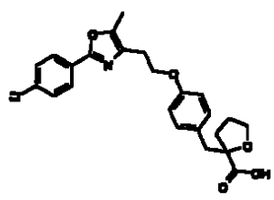
		2,82 (1 H, d, J = 13,9 Hz), 2,69 (2 H, t, J = 7,2 Hz), 2,41 (2 H, t, J = 6,7 Hz), 2,23 – 2,13 (1 H, m), 2,20 (3 H, s), 1,88 - 1,79 (1 H, m), 1,78 – 1,53 (6H, m).		
C – 76		(MeOD, 300 MHz): 8,34 – 8,32 (2 H, m a), 7,87 – 7,85 (2 H, m a), 7,8 – 7,36 (3 H, m a), 4,54 (2 H, s a), 3,83 (2 H, s a), 3,06 (1 H, d, J = 10,7 Hz), 2,93 – 2,89 (1 H, m a), 2,80 (1 H, d, J = 10,7 Hz), 2,24 (3 H, s), 1,92 - 1,77 (5 H, m).	para BR 410 $(M+H)^+$	
C – 77		(Acetona-d_6, 400 MHz): 8,08 (1H, s), 7,95 (2H, m), 7,46 (3H, m), 4,57 (2H, t, J = 6,5 Hz), 3,83 (2H, m), 3,10 (4H, m), 2,36 (3H, s), 2,20 (2H, d, J = 7,0 Hz), 1,75 (2H, m).	para BR 408 $(M)^-$	
C – 78		^{1}H RMN (DMSO-d_6, 400 MHz): 12,40 (1H, s), 7,90 (1H, dd, J = 7,8 y 1,8 Hz),	Calculado para $C_{24}H_{26}NO$	Calculado para $C_{24}H_{25}NO_5$

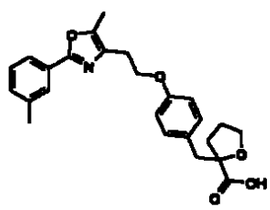
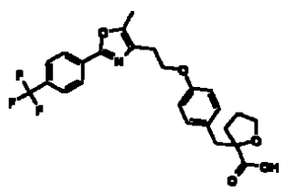
		7,51 – 7,44 (3H, m), 7,10 (2H, d, *J* = 8,3 Hz), 6,81 (2H, d, *J* = 8,6 Hz), 4,16 (2H, t, *J* = 6,8 Hz), 3,73 (2H, t, *J* = 6,8 Hz), 2,99 (1H, d, *J* = 13,9 Hz), 2,90 (2H, t, *J* = 6,6 Hz), 2,81 (1H, d, *J* = 13,9 Hz), 2,34 (3H, s), 2,11 – 2,04 (1H, m), 1,82 – 1,57 (3H, m).	s 408,1806 Encontrado: 408,1797	C 70,75, H 6,18, N 3,44. Encontrado: C 70,53, H 6,18, N 3,31
C – 79		(DMSO-d_6, 400 MHz): 7,25 – 7,24 (1H, m), 7,19 – 7,17 (2H, m), 7,06 – 7,04 (2H, m), 6,76 – 6,75 (1H, m), 6,72 – 6,70 (2H, m), 4,11 (2H, t, *J* = 6,5 Hz), 3,77 – 3,71 (2H, m), 3,00 – 2,96 (1H, m), 2,89 (6H, s), 2,87 – 2,85 (2H, m), 2,84 – 2,76 (1H, m), 2,98 (3H, s), 2,12 – 2,10 (1H, m), 1,85 – 1,82 (1H, m), 1,71 – 1,56 (2H, m)	AR calculado para $C_{26}H_{30}N_2O_6$ $(M+H)^+$ 451,2228 Encontrado: 451,2213 para BR 451 $(M+H)^+$	
C – 80		(DMSO-d_6, 300 MHz): 12,40 (1H, s), 8,14 – 8,11 (2H, m), 8,03 – 8,04 (2H, m), 7,19 – 7,16 (2H, m),	AR calculado para $C_{25}H_{24}N_2$	

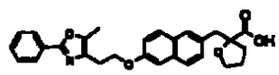
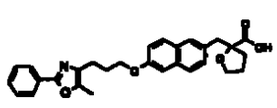
		6,89 – 6,86 (2H, m), 4,24 (2H, t, *J* = 6,5 Hz), 3,80 (2H, t, *J* = 6,6 Hz), 3,09 – 3,04 (1H, m), 3,00 (2H, t, *J* = 6,4 Hz), 2,91 – 2,86 (1H, m), 2,45 (3H, s), 2,19 – 2,13 (1H, m), 1,88 – 1,67 (3H, m)	O_5 $(M+H)^+$ 433,1758 Encontrado: 433,1741 para BR 433 $(M+H)^+$	
C – 81		(DMSO-d_6, 300 MHz): 8,10 (1H, s), 8,03 – 7,96 (4H, m), 7,48 (1H, s), 7,15 – 7,12 (2H, m), 6,85 – 6,83 (2H, m), 4,20 (2H, t, *J* = 6,5 Hz), 3,76 (2H, t, *J* = 6,5 Hz), 3,04 – 3,00 (1H, m), 2,95 (2H, t, *J* = 6,5 Hz), 2,86 – 2,82 (1H, m), 2,39 (3H, s), 2,12 (1H, m), 1,83 – 1,60 (3H, m)	para BR 451 $(M+H)^+$	
C – 82		($CDCl_3$, 300 MHz): 7,85 – 7,77 (2H, m), 7,68 – 7,63 (1H, m), 7,15 – 7,12 (2H, m), 6,82 – 6,80 (2H, m), 4,22 (2H, t, *J* = 6,5 Hz), 4,01 – 3,96 (1H, m), 3,90	calculado para $C_{25}H_{23}NO_5F_4$ $(M+H)^+$ 494,1585	

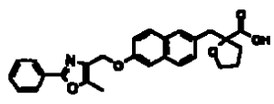
		– 3,85 (1H, m), 3,19 – 3,14 (1H, m), 2,97 (2H, t, *J* = 6,5 Hz), 2,90 – 2,85 (1H, m), 2,39 (3H, s), 2,36 – 2,32 (1H, m), 2,06 – 1,96 (1H, m), 1,87 – 1,77 (2H, m)	Encontrado: 494,1579 para BR 494 $(M+H)^+$	
C – 83		($CDCl_3$, 400 MHz): 7,87 – 7,84 (2H, d), 7,23 – 7,21 (2H, d), 7,14 – 7,12 (2H, d), 6,82 – 6,80 (2H, d), 4,19 (2H, t, *J* = 6,5 Hz), 4,01 – 3,94 (1H, m), 3,87 – 3,81 (1H, m), 3,17 – 3,14 (1H, m), 2,95 (2H, t, *J* = 6,5 Hz), 2,90 – 2,87 (1H, m), 2,38 (3H, s), 2,35 (3H, s), 2,33 – 2,30 (1H, m), 2,03 – 1,95 (1H, m), 1,87 – 1,72 (2H, m)	para BR 422 $(M+H)^+$	
C – 84		($CDCl_3$, 400 MHz): 7,92 – 7,90 (2H, m), 7,12 – 7,10 (2H, m), 6,94 – 6,92 (2H, m), 6,80 – 6,78 (2H, m), 4,18 (2H, t, *J* = 6,5 Hz), 4,02 – 3,97 (2H, m), 3,84 (3H, s), 3,17 – 3,13 (1H,	calculado para $C_{25}H_{27}NO_6$ $(M+H)^+$ 438,1911 Encontra	

		m), 2,95 (2H, t, J = 6,5 Hz), 2,90 – 2,86 (1H, m), 2,35 (3H, s), 2,03 – 2,00 (2H, m), 1,87 – 1,81 (2H, m)	do: 438,1913 para BR 438 $(M+H)^+$	
C – 85		($CDCl_3$, 400 MHz): 7,57 – 7,55 (1H, m), 7,51 – 7,49 (1H, m), 7,35 – 7,30 (1H, m), 7,10 – 7,07 (2H, m), 6,97 – 6,93 (1H, m), 6,81 – 6,78 (2H, m), 4,19 (2H, t, J = 6,5 Hz), 3,87 (3H, s), 3,04 (2H, s), 2,96 (2H, t, J = 6,5 Hz), 2,48 – 2,38 (2H, m), 2,36 (2H, s), 2,11 – 2,02 (2H, m), 1,94 – 1,85 (2H, m)		
C – 86		($CDCl_3$, 400 MHz): 7,97 (1H, s), 7,86 – 7,84 (1H, m), 7,37 – 7,35 (2H, m), 7,15 – 7,12 (2H, m), 6,82 – 6,80 (2H, m), 4,20 (2H, t, J = 6,5 Hz), 3,99 – 3,95 (1H, m), 3,88 – 3,84 (1H, m), 3,18 – 3,14 (1H, m), 2,98 (2H, t, J = 6,5 Hz), 2,90 – 2,87 (1H, m), 2,37		

		(3H, s), 2,36 – 2,31 (1H, m), 2,01 – 1,98 (1H, m), 1,88 – 1,73 (2H, m).		
C – 87		($CDCl_3$, 400 MHz): 8,24 (1H, s), 8,15 – 8,14 (1H, m), 7,66 – 7,64 (1H, m), 7,57 – 7,54 (1H, m), 7,15 – 7,13 (2H, m), 6,82 – 6,80 (2H, m), 4,21 (2H, t, *J* = 6,5 Hz), 3,88 – 3,84 (2H, m), 3,14 – 3,15 (1H, m), 2,97 (2H, t, *J* = 6,5 Hz), 2,90 – 2,86 (1H, m), 2,39 (3H, s), 2,01 – 1,98 (2H, m), 1,85 – 1,81 (2H, m)	AR calculado para $C_{25}H_{24}NO_5F_3$ $(M+H)^+$ 476,1680 Encontrado: 476,1687 para BR 477 $(M+H)^+$	
C – 88		($CDCl_3$, 400 MHz): 7,91 – 7,89 (2H, m), 7,40 – 7,38 (2H, m), 7,14 – 7,13 (2H, m), 6,81 – 6,79 (2H, m), 4,19 (2H, t, *J* = 6,5 Hz), 4,02 – 3,93 (2H, m), 3,19 – 3,14 (1H, m), 2,95 (2H, t, *J* = 6,5 Hz), 2,90 – 2,87 (1H, m), 2,36 (3H, s), 2,01 – 1,94 (2H, m), 1,87 – 1,81 (2H, m)	AR calculado para $C_{24}H_{24}NO_5Cl$ $(M+H)^+$ 442,01416 Encontrado: 442,1413 para BR	

			443 $(M+H)^+$	
C – 89		(CDCl$_3$, 400 MHz): 7,81 – 7,75 (2H, m), 7,32 – 7,28 (1H, m), 7,22 – 7,20 1H, M0, 7,14 – 7,12 (2H, m), 6,81 – 6,78 (2H, m), 4,19 (2H, t, *J* = 6,5 Hz), 3,98 – 3,81 (2H, m), 3,17 – 3,10 (1H, m), 2,96 (2H, t, *J* = 6,5 Hz), 2,91 – 2,86 (1H, m), 2,38 (3H, s), 2,36 (3H, s), 2,00 – 1,69 (4H, m)	AR calculado para $C_{25}H_{27}NO_5$ $(M+H)^+$ 422,1962 Encontrado: 442,1948 para BR 422 $(M+H)^+$	
C – 90		(CDCl$_3$, 300 MHz): 8,09 – 8,06 (2H, d), 7,69 – 7,66 (2H, d), 7,15 – 7,12 (2H, m), 6,82 – 6,79 (2H, m), 4,21 (2H, t, *J* = 6,5 Hz), 4,00 – 3,81 (2H, m), 3,18 – 3,14 (1H, m), 2,97 (2H, t, *J* = 6,5 Hz), 2,91 – 2,86 (1H, m), 2,39 (3H, s), 2,36 – 2,30 (1H, m), 2,04 – 1,72 (3H, m)	AR calculado para $C_{25}H_{24}NO_5F_3$ $(M+H)^+$ 476,1680 - Encontrado: 476,1661 para BR 475	

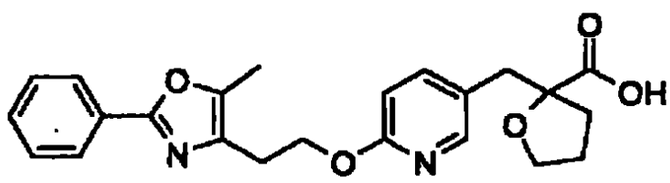
			$(M+H)^+$	
C – 91		($CDCl_3$, 400 MHz): 7,99 – 7,97 (2H, m), 7,66 (1H, d, *J* = 9,3 Hz), 7,62 – 7,59 (2H, m), 7,45 – 7,32 (4H, m), 7,11 – 7,08 (2H, m), 4,31 (2H, t, *J* = 6,6 Hz), 3,97 – 3,82 (2H, m), 3,34 (1H, d, *J* = 13,9 Hz), 3,08 – 3,01 (3H, m), 2,39 – 2,33 (4H, m), 2,08 – 2,00 (1H, m), 1,87 – 1,67 (2H, m)	para BR 458 $(M+H)^+$	
C – 92		($CDCl_3$, 400 MHz): 7,98 (2H, d, *J* = 5,8 Hz), 7,68 (1H, d, *J* = 9,1 Hz), 7,62 – 7,60 (2H, m), 7,42 – 7,33 (4H, m), 7,14 (1H, dd, *J* = 2,2, 8,8 Hz), 7,07 (1H, s), 4,06 – 3,96 (3H, m), 3,87 (1H, c, *J* = 7,5 Hz), 3,36 (1H, d, *J* = 13,9 Hz), 3,08 (1H, d, *J* = 13,9 Hz), 2,73 (2H, t, *J* = 7,1 Hz), 2,43 – 2,35 (1H, m), 2,27 (3H, m), 2,22 – 2,15 (2H, m), 2,10 – 2,01 (1H, m), 1,88	para BR 472 $(M+H)^+$	

		– 1,72 (2H, m)		
C – 93		(MeOD, 400 MHz): 7,93 – 7,90 (2H, m), 7,63 – 7,56 (3H, m), 7,41 – 7,38 (3H, m), 7,31 (1H, dd, *J* = 2,5, 8,9 Hz), 5,01 (2H, s), 3,84 – 3,73 (2H, m), 3,23 – 3,00 (2H, m), 2,39 (3H, s), 2,23 – 2,16 (1H, m), 1,96 – 1,88 (1H, m), 1,76 – 1,57 (2H, m)	para BR 444 $(M+H)^+$	

Preparaciones alternativas de los enantiómeros del ácido 2-({6-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridin-3-il}metil)tetrahidrofuran-2-carboxílico (Ejemplos C-48a y C-48b)

Ejemplo C-48a

Enantiómero 1 del ácido 2-({6-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridin-3-il}metil)tetrahidrofuran-2-carboxílico



Se añadió hidróxido de litio monohidrato (993 mg, 21,1 mmol) a una solución de (4*S*)-4-bencil-3-[2-({6-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridin-3-il}metil)tetrahidrofuran-2-il]carbonil}-1,3-oxazolidin-2-ona (600

mg, 1,06 mmol) en una mezcla de tetrahidrofurano:metanol:agua (1:1:1, 12 ml). La mezcla se agitó a 50ºC durante 4,5 horas, después se enfrió a temperatura ambiente y se agitó durante 2 días. Los componentes volátiles se retiraron por evaporación y el residuo se diluyó con agua (5 ml) y se extrajo con 1:1 hexanos:éter. La fase acuosa se acidificó a pH 5 y se extrajo con acetato de etilo. La fase orgánica se lavó con salmuera, se secó sobre sulfato de magnesio, se filtró y se evaporó. El residuo se purificó dos veces por cromatografía en columna ultrarrápida (95:4:1 de diclorometano:metanol:hidróxido de amonio), produciendo el compuesto del título en forma de un aceite incoloro (72 mg).

EMBR (*m/z*): 409 $(M+H)^+$

^{1}H RMN ($CDCl_3$, 300 MHz) 7,99-7,94 (3H, m), 7,49 (1H, dd, *J* = 2,4, 8,6 Hz), 7,44-7,36 (3H, m), 6,83 (1H, d, *J* = 8,5 Hz), 4,50 (2H, t, *J* = 6,7 Hz), 4,00-3,93 (1H, m), 3,89-3,81 (1H, m), 3,14 (1H, d, *J* = 14,1 Hz); 2,95 (2H, t, *J* = 6,7 Hz), 2,85 (1H, d, *J* = 14,1 Hz), 2,31 (3H, s), 1,99-1,73 (4H, m).

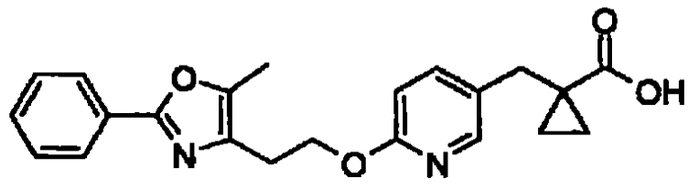
Ejemplo C-48b

Enantiómero 2 del ácido 2-({6-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridin-3-il}metil)tetrahidrofuran-2-carboxílico

El enantiómero 2 se preparó usando una secuencia de reacciones similar a las descritas para el enantiómero 1, con la excepción de que se partió de (4*R*)-4-bencil-1,3-oxazolidin-2-ona.

Ejemplo C-94

Ácido 1-{6-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-piridin-3-ilmetil}-ciclopropanocarboxílico



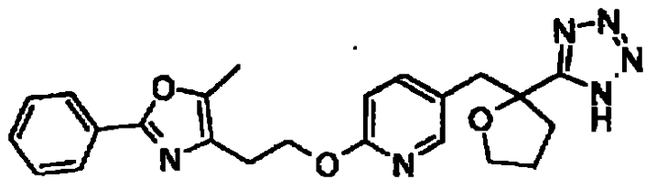
A una solución de éster *terc*-butílico del ácido 1-[6-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-piridin-3-ilmetil]-ciclopropanocarboxílico (0,2017 g, 0,4642 mmol) en anisol (1,2 ml) se le añadió ácido trifluoroacético (1,2 ml). La solución resultante se agitó a temperatura ambiente durante 3 horas y después se concentró a presión reducida. El residuo bruto se diluyó con acetato de etilo (25 ml) y agua (10 ml) y después se basificó a pH 5-6 mediante la adición de bicarbonato sódico acuso saturado. Las fases se separaron y la fase acuosa se extrajo con acetato de etilo (3 x 25 ml). Los extractos orgánicos combinados después se secaron (sulfato de magnesio anhidro), se filtraron y se concentraron al vacío para producir el producto bruto. Se obtuvo el ácido puro (0,071 g, 40%) mediante recristalización en éter dietílico/hexanos, en forma de un sólido blanco.

EMBR (*m/z*): 379 $(M+H)^+$.

^{1}H RMN (MeOD, 300 MHz): 7,89-7,83 (3H, m), 7,53 (1H, dd, *J* = 8,5, 1,9 Hz), 7,37-7,35 (3H, m), 6,60 (1H, d, *J* = 8,5 Hz), 4,39 (2H, t, *J* = 6,5 Hz), 2,87 (2H, t, *J* = 6,4 Hz), 2,73 (2H, s), 2,23 (3H, s), 1,14-1,11 (2H, m), 0,77-0,74 (2H, m).

Ejemplo C-95

2-[2-(5-Metil-2-fenil-oxazol-4-il)-etoxi]-5-[2-(1H-tetrazol-5-il)-tetrahidrofuran-2-ilmetil]-piridina



Una solución de 2-{6-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-piridin-3-ilmetil}-tetrahidro-furan-2-carbonitrilo (0,11g, 0,27 mmol), azida sódica (0,04 g, 0,54 mmol) y bromuro de cinc (0,03 g, 0,14 mmol) en agua e isopropanol (1:2, 1,24 ml) se calentó a reflujo durante 23 horas. Después de enfriar a temperatura ambiente, la reacción se interrumpió con ácido clorhídrico 3 N (0,14 ml) y acetato de etilo (2,8 ml) y la mezcla se agitó hasta que fue completamente homogénea. La fase acuosa se extrajo con acetato de etilo (3 x 50 ml) y los extractos orgánicos combinados se lavaron con agua (30 ml), se secaron (sulfato de magnesio anhidro), se filtraron y se concentraron al vacío para dar el producto bruto. El residuo se recristalizó con éter dietílico/hexanos para producir el compuesto del título (0,052 g, 44%) en forma de un sólido blanco.

Análisis elemental: Calculado $C_{22}H_{23}N_7O_3$ C 60,96, H 5,35, N 22,62. Encontrado: C 63,50, H 5,62, N 18,80.

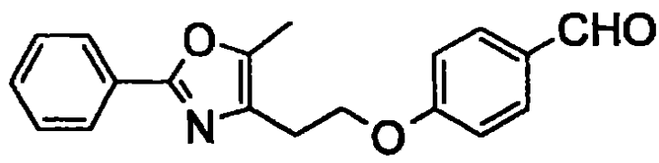
^{1}H RMN ($CDCl_3$, 300 MHz): δ 7,93 (2H, m), 7,86 (1H, s), 7,40 (3H, m), 7,11 (1H, d, J = 1,7 Hz), 6,49 (1H, d, J = 8,5 Hz), 4,42 (2H, t, J = 6,6 Hz), 3,88 (2H, m), 3,12 (2H, m), 2,92 (2H, t, J = 6,5 Hz), 2,62 (1H, m), 2,31 (3H, s), 2,23 (1H, m), 1,89 (2H, m).

EMBR (*m/z*): 433 $(M+H)^+$.

<u>Preparación de materiales de partida para los Ejemplos C-1 a C-95 (Preparaciones c-1 a c-130)</u>

Preparación c-1

4-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]benzaldehído

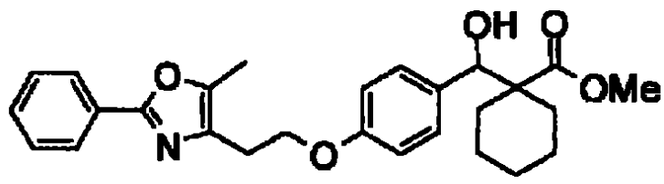


A una solución del 4-hidroxibenzaldehído (5,05g, 41,4 mmol), 2-(5-metil-2-fenil-oxazol-4-il)-etan-1-ol (8,39 g, 41,4 mmol) y trifenilfosfina (10,9 g, 41,4 mmol) en tetrahidrofurano anhidro (165 ml) en una atmósfera de nitrógeno, se le añadió gota a gota azodicarboxilato de dietilo (7,21 g, 41,4 mmol). La solución resultante se agitó a temperatura ambiente durante 8 horas, después se diluyó con agua y se extrajo con acetato de etilo. La fase orgánica se secó (sulfato de magnesio anhidro), se filtró y se evaporó al vacío. Este residuo después se purificó por cromatografía en columna ultrarrápida (hexanos a acetato de etilo) para producir el compuesto del título en forma de un sólido blanco cristalino (10,2g, 80%).

EMBR (*m/z*): 308 $(M+H)^+$.

Preparación c-2

1-(Hidroxi-[4-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]fenil]-metil)ciclohexano carboxilato de metilo



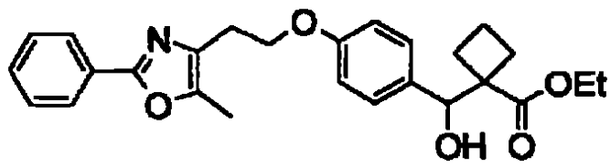
A una suspensión de cloruro de cromo(II) (1,00 g, 8,10 mmol) y yoduro de litio (0,087 g, 0,648 mmol) en tetrahidrofurano (20 ml) se le añadió 4-[2-(5-

metil-2-fenil-1,3-oxazol-4-il)etoxi]benzaldehído(Preparación 1) (1,00 g, 3,24 mmol) y 1-bromociclohexanoato de metilo (1,07 g, 4,85 mmol). La mezcla resultante se calentó a 50°C hasta que el análisis por TLC indicó que la reacción se había completado. La mezcla se enfrió a temperatura ambiente y se añadió cloruro sódico acuoso saturado (15 ml). La mezcla resultante se agitó durante 15 minutos y después se repartió entre agua y acetato de etilo. La fase orgánica se lavó con agua y se secó (sulfato de magnesio anhidro), se filtró y se evaporó. El residuo se purificó por cromatografía en columna ultrarrápida (hexanos a acetato de etilo al 50%(hexanos) para producir el compuesto del título en forma de un aceite incoloro (0,797 g, 55%).

EMBR (*m/z*): 450 $(M+H)^+$.

Preparación c-3

1-(Hidroxi-{4-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]fenil}metil)ciclobutano carboxilato de etilo

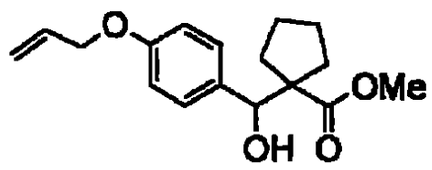


El compuesto del título se obtuvo en forma de un aceite incoloro usando procedimientos análogos a los descritos para la Preparación c-2.

EMBR (*m/z*): 436 $(M+H)^+$.

Preparación c-4

1-[[4-(Aliloxi)fenil](hidroxi)metil]ciclopentanocarboxilato de metilo

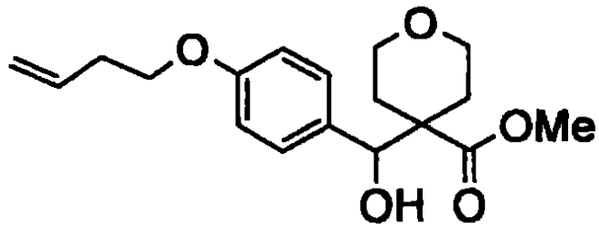


A una solución de ciclopentanoato de metilo (3,84 g, 30,0 mmol) en tetrahidrofurano (30 ml) a -78°C se le añadió gota a gota una solución de diisopropilamiduro de litio (15,0 ml de una solución 2 M en tetrahidrofurano, 30,0 mmol). La mezcla se agitó durante dos horas y después se añadió 4-aliloxibenzaldehído (2,12g 13,1mmoles). La mezcla se dejó calentar a temperatura ambiente y se agitó durante 18 horas. La mezcla se diluyó con agua y se extrajo con acetato de etilo. La fase orgánica se lavó con cloruro sódico acuoso saturado y se secó (sulfato de magnesio anhidro), se filtró y se evaporó. El residuo se purificó por cromatografía en columna ultrarrápida (hexanos a acetato de etilo al 50%/hexanos) para producir el compuesto del título en forma de un aceite incoloro (3,67 g, 97%).

EMBR (*m/z*): 273 $(M\text{-}OH)^+$.

Preparación c-5

4-[[4-(But-3-eniloxi)fenil](hidroxi)metil]tetrahidro-2H-piran-4-carboxilato de metilo

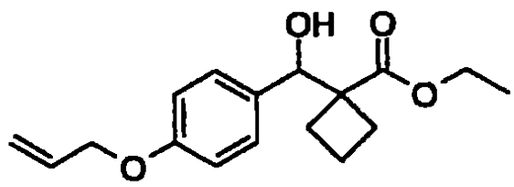


El compuesto del título se obtuvo en forma de un aceite incoloro usado procedimientos análogos a los descritos para la Preparación c-4.

EMBR (*m/z*): 273 $(M-OH)^+$.

Preparación c-6

1-[[4-(Aliloxi)fenil](hidroxi)metil]ciclobutanocarboxilato de etilo



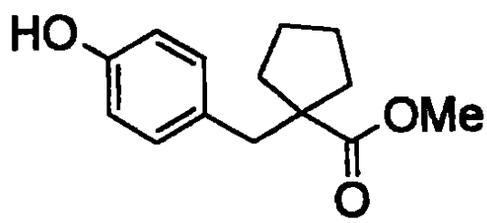
El compuesto del título se obtuvo en forma de un aceite incoloro usando procedimientos análogos a los descritos para la Preparación c-4.

EMBR (*m/z*): 289 $(M)^+$.

^{1}H RMN ($CDCl_3$, 300 MHz) 7,22 (2H, d, *J* = 8,5 Hz), 6,85 (2H, d, *J* = 8,7 Hz), 6,10-5,98 (1H, m), 5,39 (1H, ddd, *J* = 1,5, 3,2, 17,3 Hz), 5,27 (1H, ddd, *J* = 1,5, 2,8, 10,4 Hz), 4,85 (1H, d, *J* = 6,4 Hz), 4,51 (2H, dt, *J* = 1,5, 5,3 Hz), 4,13 (2H, dc, *J* = 0,9, 7,2 Hz), 3,12 (1H, d, *J* = 6,6 Hz), 2,84-2,78 (1H, m), 2,64-2,58 (1H, m), 2,35-2,29 (2H, m), 1,89-1,83 (1H, m), 1,72-1,66 (1H, m), 1,19 (3H, t, *J* = 7,0 Hz).

Preparación c-7

1-(4-Hidroxibencil)ciclopentanocarboxilato de metilo



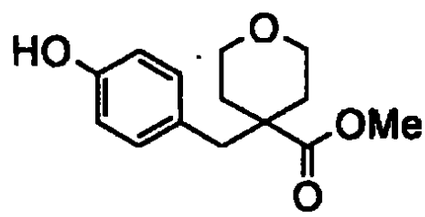
Se añadió trietilsilano (10,0 ml, 63 mmol) a una solución de 1-[[4-(aliloxi)fenil](hidroxi)metil]ciclopentanocarboxilato de metilo (Preparación c-4) (3,66 g, 12,6 mmol) en diclorometano (30 ml) y ácido trifluoroacético a

temperatura ambiente. La mezcla resultante se agitó durante 1 hora y después se evaporó al vacío y se destiló azeotrópicamente con tolueno. El residuo se disolvió en tetrahidrofurano (32 ml) y se añadieron morfolina (3,62 ml, 41,6 mmol) y tetraquis(trifenilfosfina)paladio (0) (1,46 g, 1,26 mmol). La mezcla resultante se agitó a temperatura ambiente durante 18 horas, se filtró a través de Celite y se evaporó a sequedad. El residuo se disolvió en acetato de etilo y se lavó con ácido clorhídrico 1 N y después con una solución de bicarbonato sódico saturado. La fase orgánica se secó (sulfato de magnesio anhidro), se filtró y se evaporó y el residuo se purificó por cromatografía en columna ultrarrápida (hexanos a acetato de etilo) para producir el compuesto del título en forma de un sólido blanco cristalino (1,75 g, 59%).

EMBR (*m/z*): 233 $(M)^-$.

Preparación c-8

4-(4-Hidroxibencil)tetrahidro-2H-piran-4-carboxilato de metilo

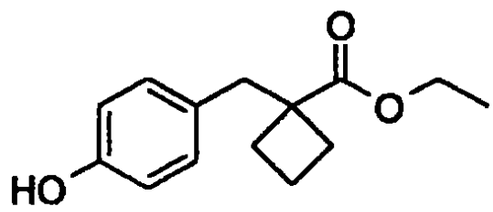


El compuesto del título se obtuvo en forma de un sólido cristalino blanco usando procedimientos análogos a los descritos para la Preparación c-7.

EMBR (*m/z*): 249 $(M)^-$.

Preparación c-9

1-(4-Hidroxibencil)ciclobutanocarboxilato de etilo



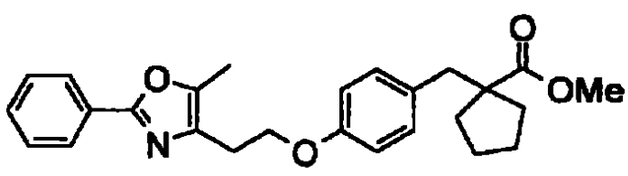
El compuesto del título se obtuvo en forma de un sólido cristalino blanco usando procedimientos análogos a los descritos para la Preparación c-7.

EMBR (*m/z*): 234 $(M)^-$.

^{1}H RMN ($CDCl_3$, 300 MHz) 6,97 (2H,d, *J* = 8,5 Hz), 6,68 (2H, d, *J* = 8,5 Hz), 5,10 (1H, s a), 4,10 (2H, c, *J* = 7,2 Hz), 3,00 (2H, s), 2,44-2,35 (2H, m), 2,07-1,99 (2H, m), 1,91-1,80 (2H, m), 1,20 (3H, t, *J* = 7,2 Hz).

Preparación c-10

1-[4-[2-(5-Metil-2-fenil-1,3-oxazol-4-il)etoxi]bencil ciclopentanocarboxilato de metilo

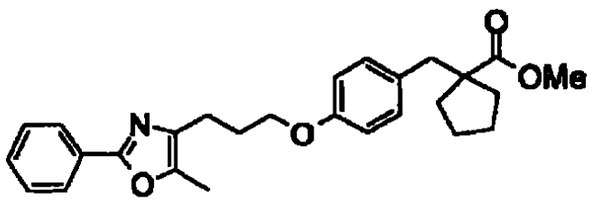


El compuesto del título se obtuvo en forma de un aceite incoloro usando procedimientos análogos a los descritos para la Preparación c -1 c-7.

EMBR (*m/z*): 249 $(M)^-$.

Preparación c-11

1-[4-[3-(5-Metil-2-fenil-1,3-oxazol-4-il)propoxi]bencil]ciclopentanocarboxilato de metilo

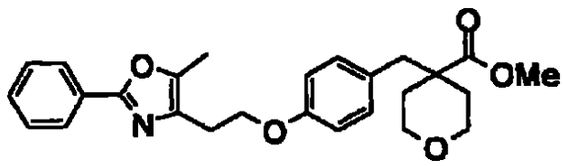


El compuesto del título se obtuvo en forma de un aceite incoloro usando procedimientos análogos a los descritos para la Preparación c -1 c-7.

EMBR (*m/z*): 434 $(M+H)^+$.

Preparación c-12

4-{4-[2-(5-Metil-2-fenil-1,3-oxazol-4-il)etoxi]bencil}tetrahidro-2*H*-piran-4-carboxilato de metilo

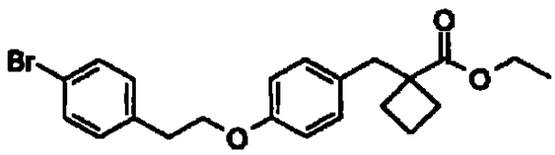


El compuesto del título se obtuvo en forma de un aceite incoloro usando procedimientos análogos a los descritos para la Preparación c -1 c-7.

EMBR (*m/z*): 436 $(M+H)^+$.

Preparación c-13

1-{4-[2-(4-Bromofenil)etoxi]bencil}ciclobutanocarboxilato de etilo



El compuesto del título se obtuvo en forma de un aceite incoloro usando procedimientos análogos a los descritos para la Preparación c -1 c-7.

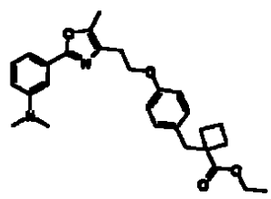
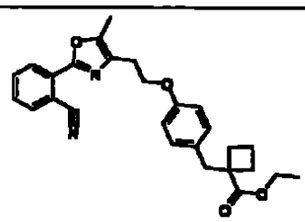
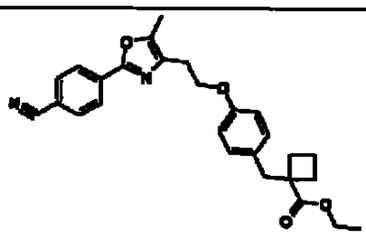
EMBR (*m/z*): 417 $(M)^+$.

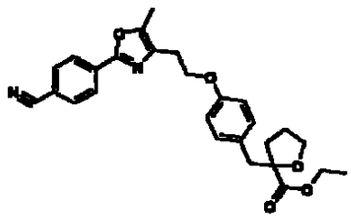
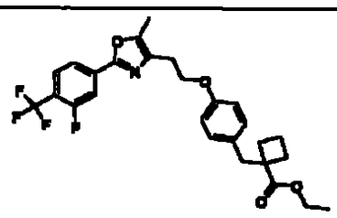
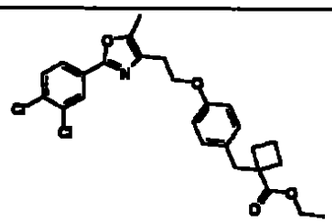
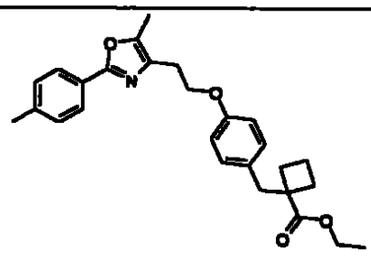
^1H RMN($CDCl_3$, 300 MHz) 7,36 (2H, d, J = 8,3 Hz), 7,08 (2H, d, J = 8,3 Hz),

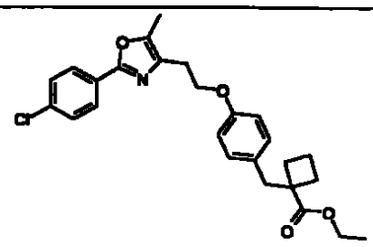
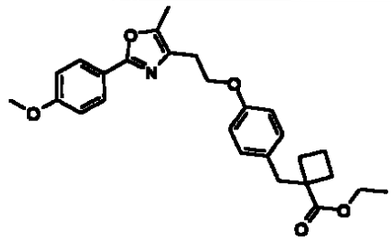
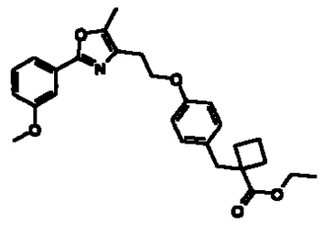
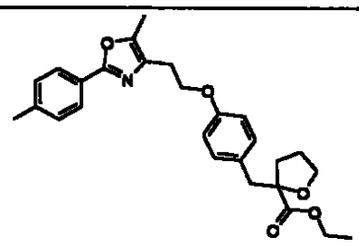
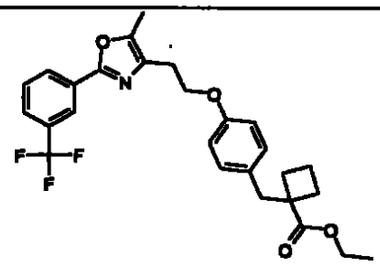
6,96 (2H, d, J = 8,7 Hz), 6,70 (2H, d, J = 8,7 Hz), 4,04 (2H, t, J = 6,8 Hz), 4,03 (2H, c, J = 7,2 Hz), 2,95 (2H, t, J = 6,8 Hz), 2,94 (2H, s), 2,37-2,27 (2H, m), 2,00-1,91 (2H, m), 1,84-1,73 (2H, m), 1,14 (3H, t, J = 7,2 Hz).

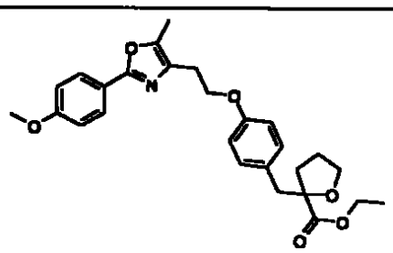
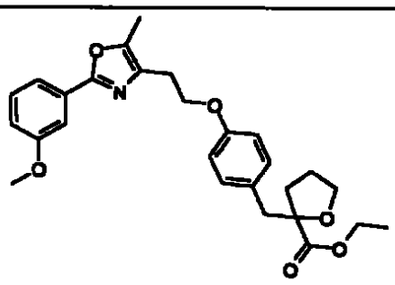
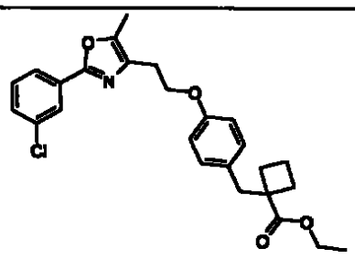
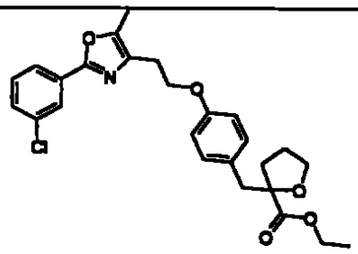
Preparaciones c-14 a c-35

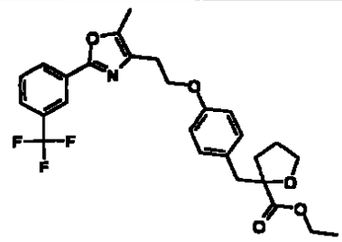
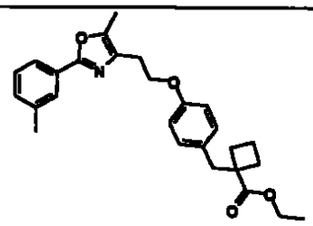
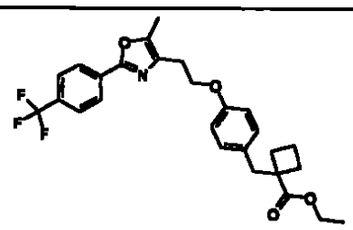
Las Preparaciones c-14 a c-35 se prepararon usando procedimientos análogos a los usados para la Preparación c-1

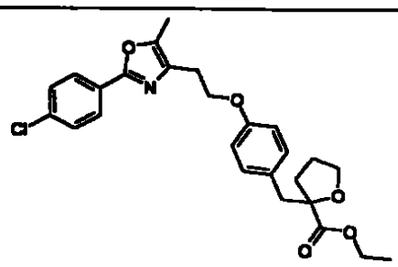
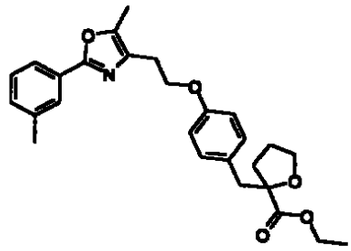
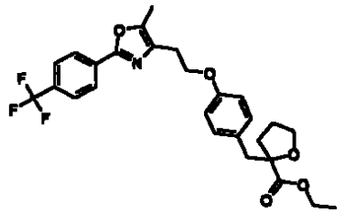
Prep Nº	Estructura	^{1}H RMN	EM (*m/z*) (BR o AR)
c-14			Para BR 463 $(M+H)^+$
c-15		($CDCl_3$, 300 MHz) 8,14-8,11 (1H, m), 7,78-7,75 (1H, m), 7,67-7,62 (1H, m), 7,51-7,45 (1H, m), 7,04-7,01 (2H, m), 6,80-6,78 (2H, m), 4,23 (2H, t, J = 6,5), 4,13-4,06 (2H, c, J = 7,1 Hz), 3,00 (2H, t, J = 3,3 Hz), 2,42 (3H, s), 2,40-2,36 (2H, m), 2,05-2,00 (2H, m), 1,87-1,84 (2H, m), 1,21 (3H, t, J = 7,1 Hz).	Para BR 446 $(M+H)^+$
c-16		($CDCl_3$, 300 MHz) 8,07-8,04 (2H, m), 7,71-7,68 (2H, m), 7,03-7,01 (2H, m), 6,78-6,75 (2H, m), 4,19 (2H, t, J = 6,5 Hz), 4,13-4,06 (3H, m), 2,99 (2H, s) 2,96 (2H, t, J = 6,5 Hz), 2,39 (3H, s), 2,38-2,34 (2H, m), 2,02-1,99 (2H, m), 1,87-1,82	Para BR 445 $(M+H)^+$

		(2H, m), 1,20 (3H, t, J = 6,9 Hz).	
c-17		($CDCl_3$, 300 MHz) 8,08-8,05 (2H, m), 7,71-7,68 (2H, m), 7,16-7,13 (2H, m), 6,80-6,77 (2H, m), 5,01-4,92 (2H, m), 4,21 (2H, t, J = 6,5 Hz), 3,92-3,85 (2H, m), 3,15-3,08 (1H, m), 2,97 (2H, t, J = 6,4 Hz), 2,95-2,88 (1H, m), 2,40 (3H, s), 2,28-2,21 (1H, m), 2,04 (3H,s), 1,91-1,86 (2H, m).	Para BR 461 $(M+H)^+$
c-18			Para BR 506 $(M+H)^+$
c-19		($CDCl_3$, 300 MHz) 8,05-8,04 (1H, m), 7,79-7,75 (1H, m), 7,47-7,44 (1H, d), 7,03-7,00 (2H, m), 6,76-6,75 (2H, m), 4,18 (2H, t, J = 6,5 Hz), 4,13-4,06 (2H, c, J = 7,1 Hz), 3,00 (2H, s), 2,94 (2H, t, J = 6,5 Hz), 2,49-2,36 (2H, m), 2,35 (3H, s), 2,04-1,97 (2H, m), 1,87-1,81(2H, m), 1,20 (3H, t, J = 7,1 Hz).	Para BR 489 $(M+H)^+$
c-20			Para BR 435 $(M+H)^+$

c-21			Para BR 455 $(M+H)^+$
c-22			Para BR 450 $(M+H)^+$
c-23		($CDCl_3$, 400 MHz) 7,57-7,56 (1H, m), 7,51-7,50 (1H, m), 7,34-7,30 (1H, m), 7,03-7,01 (2H, m), 6,96-6,93 (1H, m), 6,80-6,77 (2H, m), 4,20 (2H, t, *J* = 6,6 Hz), 4,12-4,07 (2H, c, *J* = 7,0 Hz), 3,86 (3H, s), 3,00 (2H, s), 2,95 (2H, t, *J* = 6,5 Hz), 2,42-2,37 (2H, m), 2,35 (3H, m), 2,05-1,98 (2H, m), 1,88-1,81 (2H, m).	Para BR 450 $(M+H)^+$
c-24			Para BR 450 $(M+H)^+$
c-25			Para BR 488 $(M+H)^+$

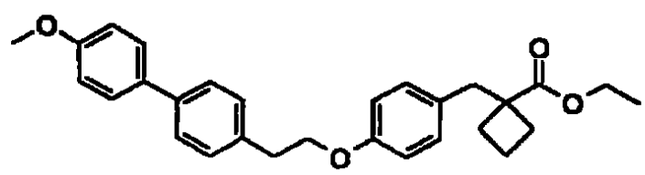
c-26			Para BR 466 $(M+H)^+$
c-27		($CDCl_3$, 400 MHz) 7,57-7,56 (1H, m), 7,51-7,50 (1H, m), 7,34-7,30 (1H, m), 7,03-7,01 (2H, m), 6,96-6,93 (1H, m), 6,80-6,77 (2H, m), 4,20 (2H, t, *J* = 6,5 Hz), 4,12-4,07 (2H, c, *J* = 7,0 Hz), 3,86 (3H, s), 3,00 (2H, s), 2,95 (2H, t, *J* = 6,5 Hz), 2,42-2,37 (2H, m), 2,35 (3H, s), 2,05-1,98 (2H, m), 1,86-1,81 (2H, m), 1,20 (3H, t, *J* = 7,0 Hz).	Para BR 450 $(M+H)^+$
c-28		($CDCl_3$, 400 MHz) 7,97 (1H, s), 7,86-7,83 (1H, s), 7,35-7,33 (2H, m), 7,03-7,01 (2H, m), 6,79-6,77 (2H, m), 4,19 (2H, t, *J* = 6,5 Hz), 4,12-4,07 (2H, c, *J* = 7,0 Hz), 3,00 (2H, s), 2,95 (2H, t, *J* = 6,5 Hz), 2,42-2,38 (2H, m), 2,35 (3H, s), 2,05-1,99 (2H, m), 1,91-1,82 (2H, m), 1,20 (3H, t, *J* = 7,0 Hz).	Para BR 454 $(M+H)^+$
c-29		($CDCl_3$, 400 MHz) 7,97 (1H, s), 7,87-7,84 (1H, m), 7,36-7,35 (2H, m), 7,16-7,14 (2H, m), 6,81-6,78 (2H, m), 4,21 (2H, t, *J* = 6,5 Hz), 4,15-4,10 (c, *J* = 7,0 Hz), 3,91-3,87 (2H, m), 3,14-3,10 (1H, m), 2,96 (2H, t, *J* = 6,5 Hz), 2,93-2,90 (1H, m), 2,37 (3H, s), 2,26-2,12 (2H, m), 1,89-1,76	Para BR 470 $(M+H)^+$

		(2H, m), 1,21 (3H, t, J = 7,0 Hz).	
c-30		($CDCl_3$, 400 MHz) 8,24 (1H, s), 8,16-8,14 (1H, m), 7,66-7,64 (1H, m), 7,57-7,53 (1H, m), 7,16-7,14 (2H, m), 6,81-6,79 (2H, m), 4,22 (2H, t, J = 6,5 Hz), 4,15-4,10 (2H, c, J = 7,0 Hz), 3,93-3,86 (2H, m), 3,14-3,11 (1H, m), 2,97 (2H, t, J = 6,5 Hz), 2,93-2,90 (1H, m), 2,39 (3H, s), 2,26-2,20 (2H, m), 1,91-1,78 (2H, m), 1,21 (3H, t, J = 7,0 Hz).	Para BR 504 $(M+H)^+$
c-31		($CDCl_3$, 300 MHz) 7,81-7,75 (2H, m), 7,32-7,27 (1H, m), 7,21-7,19 (1H, m), 7,03-7,00 (2H, m), 6,78-6,76 (2H, m), 4,19 (2H, t, J = 6,5 Hz), 4,13-4,06 (2H, c, J = 7,1 Hz), 3,00 (2H, s), 2,95 (2H, t, J = 6,5 Hz), 2,43-2,40 (2H, m), 2,37 (3H, s), 2,35 (3H, s), 2,07-1,97 (2H,m), 1,89-1,79 (2H, m), 1,19 (3H, t, J = 7,1 Hz).	Para BR 434 $(M+H)^+$
c-32		($CDCl_3$, 300 MHz) 8,09-8,06 (2H, m), 7,69-7,66 (2H, m), 7,04-7,01 (2H, m), 6,80-6,77 (2H, m), 4,21 (2H, t, J = 6,5 Hz), 4,15-4,06 (2H, m), 3,00 (2H, s), 2,96 (2H, t, J = 6,5 Hz), 2,43-2,34 (5H, m), 2,01-1,97 (2H, m), 1,92-1,79 (2H, m), 1,20 (3H, t, J = 7,1 Hz).	Para BR 488 $(M+H)^+$

c-33			Para BR 470 $(M+H)^+$
c-34		($CDCl_3$, 300 MHz) 7,81-7,75 (1H, m), 7,33-7,27 (2H, m), 7,22-7,19 (1H, m), 7,16-7,13 (2H, m), 6,81-6,78 (2H, m), 4,20 (2H, t, *J* = 6,7 Hz), 4,16-4,09 (2H, c, *J* = 7,1 Hz), 3,94-3,82 (2H, m), 3,14-3,08 (1H, m), 2,98-2,94 (2H, t, *J* = 6,5 Hz), 2,94-2,88 (1H, m), 2,38 (3H, s), 2,36 (3H, s), 2,27-2,19 (1H,m), 1,92-1,74 (2H, m), 1,68-1,62 (1H, m), 1,21 (3H, t, *J* = 7,1 Hz).	Para BR 450 $(M+H)^+$
c-35		($CDCl_3$, 300 MHz) 8,09-8,07 (2H, m), 7,69-7,66 (2H, m), 7,16-7,14 (2H, m), 6,81-6,78 (2H, m), 4,21 (2H, t, *J* = 6,5 Hz), 4,16-4,09 (2H, c, *J* = 7,1 Hz), 3,95-3,83 (2H, m), 3,15-3,10 (1H, m), 2,97 (2H, t, *J* = 6,5 Hz), 2,94-2,89 (1H, m), 2,39 (3H, s), 2,27-2,18 (1H, m), 1,92-1,61 (3H, m), 1,21 (3H, t, *J* = 7,1 Hz).	Para BR 504 $(M+H)^+$

Preparación c-36

1-[4-[2-(4'-Metoxi-1,1'-bifenil-4-il)etoxi]bencil]ciclobutanocarboxilato de etilo



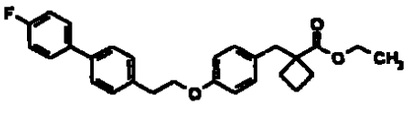
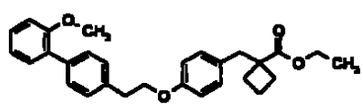
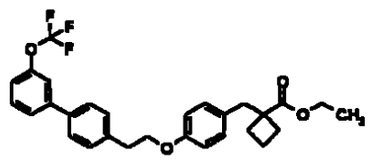
A una solución de 1-[4-[2-(4-bromofenil)etoxi]bencil]ciclobutanocarboxilato de etilo (Preparación c-13) (0,25 g, 0,5990 mmol), tetraquis(trifenilfosfina)paladio (0) (0,1252 g, 0,6589 mmol), benceno (1,6 ml) y carbonato sódico acuoso 2 M (0,8 ml) en una atmósfera de nitrógeno se le añadió una solución del ácido bórico (0,8640 mmol, 1,1 equiv.) en etanol (0,4 ml). La mezcla resultante se desgasificó y después se calentó a reflujo durante 16 horas, seguido de refrigeración a temperatura ambiente. A esto después se le añadió gota a gota peróxido de hidrógeno acuoso al 30% (0,04 ml) y la solución resultante se agitó a temperatura ambiente durante 1 hora. Después la solución se extrajo con acetato de etilo (3 x 100 ml) y los extractos orgánicos combinados se lavaron con cloruro sódico acuoso saturado 8100 ml), se secaron (sulfato de magnesio anhidro), se filtraron y se concentraron al vacío para producir el producto bruto. El residuo se purificó por cromatografía en columna ultrarrápida (hexanos a acetato de etilo al 40%/hexanos) para producir el producto puro en forma de un aceite incoloro.

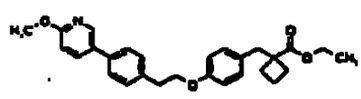
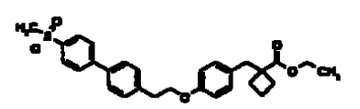
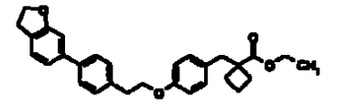
EMBR (*m/z*): 462 $(M+H_2O)^+$.

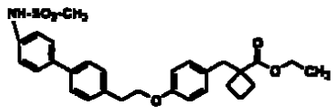
^{1}H RMN ($CDCl_3$, 300 MHz) 7,51 (2H, d, *J* = 5,7 Hz), 7,49 (2H, d, *J* = 4,7 Hz), 7,32 (2H, d, *J* = 8,1 Hz), 7,03 (2H, d, *J* = 8,5 Hz), 6,97 (2H, d, *J* = 8,9 Hz), 6,80 (2H, d, *J* = 8,5 Hz), 4,15 (1H, t, *J* = 7,2 Hz), 4,10 (2H, c, *J* = 7,2 Hz), 3,84 (3H, s), 3,10 (2H, t, *J* = 7,1 Hz), 3,01 (2H, s), 2,43-2,34 (2H, m), 2,07-1,98 (2H, m), 1,90-1,80 (2H, m), 1,20 (3H, t, *J* = 7,2 Hz).

Preparaciones c-37 a c-43

Las Preparaciones c-37 a c-43 se prepararon usando procedimientos análogos a los usados para la Preparación c-36

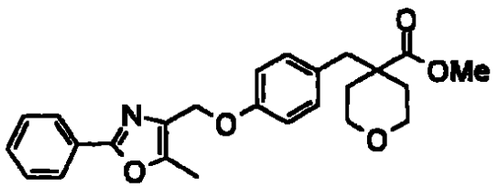
Prep Nº	Estructura	^{1}H RMN	EM (*m/z*) (BR o AR)
c-37		($CDCl_3$, 300 MHz) 7,46 (2H, d, *J* = 8,9 Hz), 7, 41 (2H, d, *J* = 8,3 Hz), 7,27 (2H, d, *J* = 8,1 Hz), 7,03 (2H, d, *J* = 8,9 Hz), 6,97 (2H, d, *J* = 8,5 Hz), 6,73 (2H, d, *J* = 8,7 Hz), 4,09 (2H, t, *J* = 7,0 Hz), 4,03 (2H, c, *J* = 7,0 Hz), 3,03 (2H, t, *J* = 7,0 Hz), 2,94 (2H, s), 2,37-2,27 (2H, m), 2,00-1,91 (2H, m), 1,83-1,72 (2H, m), 1,13 (3H, t, *J* = 7,1 Hz).	Para BR 433 $(M+H)^+$
c-38		($CDCl_3$, 300 MHz) 7,48 (2H, d, *J* = 8,1 Hz), 7, 34-7,29 (4H, m), 7,05 (2H, d, *J* = 8,7 Hz), 6,99 (2H, d, *J* = 8,5 Hz), 6,81 (2H, d, *J* = 8,7 Hz), 4,18 (2H, t, *J* = 7,3 Hz), 4,11 (2H, c, *J* = 7,0 Hz), 3,81 (3H, s), 3,12 (2H, t, *J* = 7,3 Hz), 3,02 (2H, s), 2,44-2,35 (2H, m), 2,08-1,99 (2H, m), 1,91-1,80 (2H, m), 1,21 (3H, t, *J* = 7,0 Hz).	Para BR 467 $(M+Na)^+$
c-39		($CDCl_3$, 300 MHz) 7,53-7,49 (3H, m), 7,44 (2H, t, *J* = 7,9 Hz), 7, 38 (2H, t, *J* = 7,9 Hz), 7,09 (1H, dm, *J* = 8,0 Hz), 7,04 (2H, d, *J* = 8,5 Hz), 6,80 (2H, d, *J* = 8,5 Hz), 4,17 (2H, t, *J* = 7,0 Hz), 4,10 (2H, c, *J* = 7,0 Hz), 3,12 (2H, t, *J*	Para BR 499 $(M+H)^+$

		= 7,0 Hz), 3,01 (2H, s), 2,44-2,35 (2H, m), 2,07-1,98 (2H, m), 1,90-1,83 (2H, m), 1,21 (3H, t, *J* = 7,2 Hz).	
c-40		($CDCl_3$, 300 MHz) 8,36 (1H, s), 7,77 (1H, dd, *J* = 2,5 y 8,7 Hz), 7, 46 (2H, d, *J* = 8,1 Hz), 7,35 (2H, d, *J* = 8,1 Hz), 7,03 (2H, d, *J* = 8,3 Hz), 6,81 (2H, d, *J* = 8,3 Hz), 6,79 (2H, d, *J* = 8,3 Hz), 4,16 (2H, t, *J* = 6,8 Hz), 4,09 (2H, c, *J* = 7,2 Hz), 3,97 (3H, s), 3,10 (2H, t, *J* = 7,0 Hz), 3,00 (2H, s), 2,43-2,33 (2H, m), 2,06-1,97 (2H, m), 1,89-1,79 (2H, m), 1,20 (3H, t, *J* = 7,1 Hz).	Para BR 446 $(M+H)^+$
c-41		($CDCl_3$, 300 MHz) 7,99 (2H, d, *J* = 8,1 Hz), 7, 75 (2H, d, *J* = 8,1 Hz), 7,56 (2H, d, *J* = 8,1 Hz), 7,40 (2H, d, *J* = 7,9 Hz), 7,03 (2H, d, *J* = 8,5 Hz), 6,79 (2H, d, *J* = 8,5 Hz), 4,17 (2H, t, *J* = 6,8 Hz), 4,09 (2H, c, *J* = 7,2 Hz), 3,13 (2H, t, *J* = 6,9 Hz), 3,08 (3H, s), 3,00 (2H, s), 2,43-2,33 (2H, m), 2,06-1,97 (2H, m), 1,90-1,79 (2H, m), 1,20 (3H, t, *J* = 7,2 Hz).	Para BR 511 $(M+Na)^+$
c-42		($CDCl_3$, 300 MHz) 7,48 (2H, d, *J* = 8,3 Hz), 7, 41 (1H, s), 7,34-7,31 (1H, m), 7,31 (2H, d, *J* = 8,3 Hz), 7,04 (2H, d, *J* = 8,7 Hz), 6,85 (1H, d, *J* = 8,5 Hz), 6,80 (2H, d, *J* = 8,5 Hz), 4,61 (2H, d, *J* = 8,7 Hz), 4,16 (2H, t, *J* = 7,2 Hz), 4,10 (2H, c, *J* = 7,2 Hz), 3,27 (2H, t, *J*	Para BR 479 $(M+Na)^+$

		= 8,7 Hz), 3,10 (2H, t, *J* = 7,0 Hz), 3,01 (2H, s), 2,44-2,35 (2H, m), 2,07-1,99 (2H, m), 1,91-1,83 (2H, m), 1,21 (3H, t, *J* = 7,2 Hz).	
c-43		($CDCl_3$, 300 MHz) 7,57 (2H, d, *J* = 8,5 Hz), 7, 50 (2H, d, *J* = 8,5 Hz), 7,35 (2H, d, *J* = 8,5 Hz), 7,27 (2H, d, *J* = 8,5 Hz), 7,03 (2H, d, *J* = 8,7 Hz), 6,79 (2H, d, *J* = 8,7 Hz), 6,37 (1H, sa), 4,16 (2H, t, *J* = 7,0 Hz), 4,09 (2H, c, *J* = 7,0 Hz), 3,11 (2H, d, *J* = 7,0 Hz), 3,04 (3H, s), 3,00 (2H, s), 2,43-2,33 (2H, m), 2,06-1,97 (2H, m), 1,89-1,79 (2H, m), 1,20 (3H, t, *J* = 7,2 Hz).	Para BR 508 $(M)^+$

Preparación c-44

4-[4-[(5-Metil-2-fenil-1,3-oxazol-4-il)metoxi]bencil]tetrahidro-2H-piran-4-carboxilato de metilo



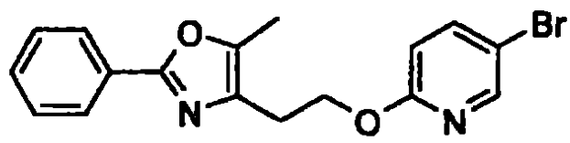
Una solución de 4-(4-hidroxibencil)tetrahidro-2H-piran-4-carboxilato de metilo (Preparación c-8) (0,500 g, 2,0 mmol), carbonato de cesio (1,96 g, 6,0 mmol) y cloruro (0,458 g, 2,2 mmol) en acetonitrilo se calentó a 140°C en un sintetizador de microondas durante 10 minutos. La mezcla se enfrió, se filtró y el filtrado se evaporó. El residuo se purificó por cromatografía en columna

ultrarrápida (hexanos a acetato de etilo) para producir el compuesto del título en forma de un sólido cristalino (0,827 g, 98%).

EMBR (m/z): 422 $(M+H)^+$.

Preparación c-45

5-Bromo-2-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridina



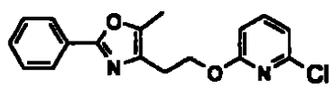
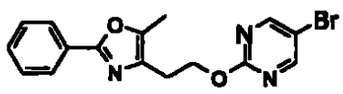
A una solución de 2,5-dibromo-piridina (5 g, 21,1060 mmol) y 2-(5-metil-2-fenil-oxazol-4-il)-etanol (5,1472 g, 25,3271 mmol) en tetrahidrofurano anhidro (85 ml) en una atmósfera de nitrógeno se le añadió terc-butóxido potásico (2,8422 g, 25,3271 mmol). La mezcla resultante se calentó a reflujo durante 16 horas y después se dejó enfriar a temperatura ambiente. La mezcla se evaporó a aproximadamente 20 ml y se repartió entre cloruro amónico acuoso saturado (50 ml) y acetato de etilo (50 ml). Las capas se separaron y la capa acuosa se extrajo con acetato de etilo (2 x 50 ml). Los extractos orgánicos combinados después se lavaron con agua (2 x 50 ml), cloruro sódico acuoso saturado (50 ml), se secaron (sulfato de magnesio anhidro), se filtraron y se concentraron al vacío para producir el producto bruto. El residuo se purificó por cromatografía en columna ultrarrápida (hexanos a acetato de etilo al 20%/hexanos) para producir un sólido blanco cristalino (6,3 g, 83%).

EMBR (*m/z*): 359 $(M)^+$.

^{1}H RMN ($CDCl_3$, 400 MHz) 8,17 (1H, d, J = 2,0 Hz), 7,96 (2H, dd, J = 2,0, 8,1 Hz), 7,61 (1H, dd, J = 2,7, 8,7 Hz), 7,43-7,38 (3H, m), 6,62 (1H, d, J = 8,6 Hz), 4,52 (2H, t, J = 6,8 Hz), 2,96 (2H, t, J = 6,8 Hz), 2,32 (3H, s).

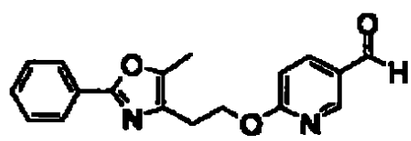
Preparaciones c-46 a c-47

Las Preparaciones c-46 a c-47 se prepararon por el procedimiento general de la Preparación c-45

Prep Nº	Estructura	^{1}H RMN	EM (*m/z*) (BR o AR)
c-46		($CDCl_3$, 400 MHz) 7,97 (2H, dd, *J* = 8,0, 7,6 Hz), 7, 49 (1H, dd, *J* = 8,1, 7,6 Hz), 7,43-7,38 (3H, m), 6,87 (1H, d, *J* = 7,6 Hz), 6,62 (1H, d, *J* = 8,1 Hz), 4,55 (2H, t, *J* = 7,0 Hz), 2,97 (2H, t, *J* = 7,0 Hz), 2,34 (3H, s).	para BR 315 $(M+H)^+$
c-47		($CDCl_3$, 300 MHz) 8,51(2H, s), 7,97-7,94 (2H, m), 7,45-7,38 (3H, m), 4,61 (2H, t, *J* = 6,9 Hz), 3,01 (2H, t, *J* = 6,9 Hz), 2,35 (3H, s)	para BR 361 $(M+H)^+$

Preparación c-48

6-[2-(5-Metil-2-fenil-1,3-oxazol-4-il)etoxi]nicotinaldehído



A una solución de butillitio (27,4 ml de una solución 1,6 M en hexanos, 43,8199 mmol) en tetrahidrofurano anhidro (200 ml) en una atmósfera de nitrógeno se le añadió una solución de 5-bromo-2-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridina (Preparación c-45) (14,31 g, 39,8363 mmol) en

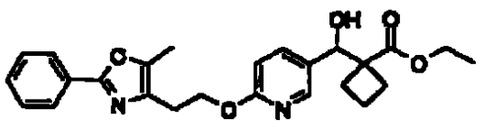
tetrahidrofurano anhidro (170 ml) y éter dietílico anhidro (170 ml) durante un periodo de 45 minutos. A esta solución después se le añadió gota a gota *N,N*-dimetilformamida anhidra (5,7 ml) y la mezcla se agitó a 0°C durante 1 hora. La reacción se interrumpió por la adición de cloruro amónico acuoso saturado (250 ml) y después de acetato de etilo (250 ml). Las capas resultantes se separaron y la capa acuosa se extrajo con acetato de etilo (2 x 250 ml). Los extractos orgánicos combinados se lavaron con agua (2 x 250 ml), cloruro sódico acuoso saturado (250 ml, se secaron (sulfato de magnesio anhidro), se filtraron y se concentraron al vacío para producir el producto bruto. El residuo se purificó por cromatografía en columna ultrarrápida (hexanos a acetato de etilo al 50%/hexanos) para producir un sólido cristalino amarillo pálido (7,17 g, 58%).

EMBR (*m/z*): 309 $(M+H)^+$.

^{1}H RMN ($CDCl_3$, 300 MHz) 9,93 (1H, s), 8,61 (1H, d, *J* = 2,3 Hz), 8,04 (1H, dd, *J* = 2,5, 8,7 Hz), 7,98-7,95 (2H, m), 7,43-7,39 (3H, m), 6,81 (1H, d, *J* = 8,7 Hz), 4,68 (2H, t, *J* = 6,8 Hz), 3,00 (2H, t, *J* = 6,8 Hz), 2,34 (3H, s).

Preparación c-49

1-(Hidroxi-{6-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridin-3-il}metil)ciclobutanocarboxilato de etilo



A una solución de 6-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]nicotinaldehído (Preparación c-48) (0,65 g, 2,1081 mmol), cloruro de cromo (II) (1 g, 8,1367 mmol) y yoduro de litio (0,0784 g, 0,5859 mmol) en tetrahidrofurano anhidro (15 ml) en una atmósfera de nitrógeno se le añadió

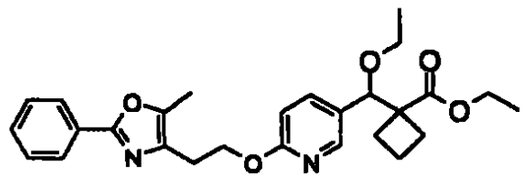
gota a gota una solución de éster etílico del ácido 1-bromo-ciclobutanocarboxílico (0,79 ml, 4,8821 mmol) en tetrahidrofurano anhidro (5 ml). La mezcla resultante se agitó a 50°C durante 3 horas y se dejó enfriar a temperatura ambiente. La solución después se inactivó por la adición de agua (50 ml) y la capa orgánica se separó y se lavó adicionalmente con agua (2 x 50 ml), cloruro sódico acuoso saturado (50 ml), se secó (sulfato de magnesio anhidro), se filtró y se concentró al vacío para producir el producto bruto. El residuo se purificó por cromatografía en columna ultrarrápida (acetato de etilo al 50%/hexanos a acetato de etilo) para producir un aceite amarillo (0,3422 g, 37%).

EMBR (*m/z*): 437 $(M+H)^+$.

^{1}H RMN ($CDCl_3$, 400 MHz) 8,05 (1H, d, *J* = 2,3 Hz), 7,98-7,95 (2H, m), 7,56 (1H, dd, *J* = 2,5, 8,7 Hz), 7,44-7,37 (3H, m), 6,67 (1H, d, *J* = 8,7 Hz), 4,85 (1H, d, *J* = 6,6 Hz), 4,54 (2H, t, *J* = 6,6 Hz), 4,18-4,07 (2H, m), 3,31 (1H, s a), 2,96 (2H, t, *J* = 6,7 Hz), 2,46-2,30 (2H, m), 2,32 (3H, s), 2,21-2,12 (1H, m), 1,97-1,85 (1H, m), 1,79-1,65 (2H, m), 1,21 (3H, t, *J* = 7,2 Hz).

Preparación c-50

Éster etílico del ácido 1-(etoxi-[6-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-piridin-3-il]-metil)-ciclobutanocarboxílico



A una solución de éster etílico del ácido 1-(hidroxi-[6-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-piridin-3-il]-metil)-ciclobutanocarboxílico (0,1711 g, 0,3920

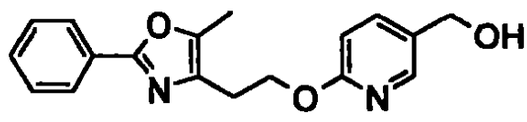
mmol)en acetonitrilo seco (2 ml) se le añadió óxido de plata(I) (1,8168 g, 7,8396 mmol) y yodoetano (0,64 ml, 7,8396 mmol). La mezcla resultante se agitó durante 5 días y se concentró a presión reducida para producir el producto bruto y se recuperó el material de partida restante. El residuo se purificó por cromatografía en columna ultrarrápida (hexanos a acetato de etilo) para producir el éster puro (0,0474 g, 26%) en forma de un aceite incoloro.

EMBR (*m/z*): 465 $(M+H)^+$.

^{1}H RMN ($CDCl_3$, 400 MHz): 8,05 (1H, d, *J* = 2,3 Hz), 7,98-7,95 (2H, m), 7,56 (1H, dd, *J* = 2,5, 8,7 Hz), 7,44-7,37 (3H, m), 6,67 (1H, d, *J* = 8,7 Hz), 4,65 (1H, m), 4,54 (2H, t, *J* = 6,6 Hz), 4,18-4,07 (2H, m), 4,06 (2H, c, *J* = 7,1 Hz), 2,96 (2H, t, *J* = 6,7 Hz), 2,46-2,30 (2H, m), 2,32 (3H, s), 2,21-2,12 (1H, m), 1,97-1,85 (1H, m), 1,79-1,65 (2H, m), 1,42 (3H, t, *J* = 7,1 Hz), 1,21 (3H, t, *J* = 7,2 Hz).

Preparación c-51

{6-[2-(5-Metil-2-fenil-1,3-oxazol-4-il)etoxi]piridin-3-il}metanol



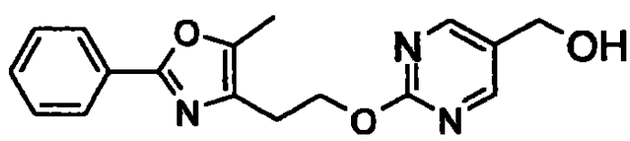
Se añadió en porciones borohidruro sódico (0,480 g, 12,7 mmol) a una solución de 6-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]nicotinaldehído (Preparación c-48) (1,30 g, 4,22 mmol)en metanol (40 ml) a temperatura ambiente. La mezcla se agitó durante 30 minutos y después se evaporó. El residuo se repartió entre cloruro amónico acuoso saturado y acetato de etilo. la fase orgánica se lavó con cloruro sódico acuoso saturado y se secó (sulfato de magnesio anhidro), se filtró y se evaporó para dar el compuesto del título en forma de un sólido blanco cristalino (1,24 g, 100%).

EMBR (*m/z*): 311 (M+H)+.

^{1}H RMN ($CDCl_3$, 300 MHz) 8,11 (1H, d, *J* = 2,6 Hz), 8,00-7,95 (2H, m), 7,60 (1H, dd, *J* = 2,5, 8,5 Hz), 7,45-7,38 (3H, m), 6,72 (1H, d, *J* = 8,5 Hz), 4,61 (2H, s a), 4,56 (2H, t, *J* = 6,8 Hz), 2,98 (2H, t, *J* = 6,8 Hz), 2,33 (3H, s).

Preparación c-52

{2-[2-(5-Metil-2-fenil-oxazol-4-il)-etoxi]-pirimidin-5-il}-metanol



Una solución de 5-bromo-2-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-pirimidina (1,0 g, 2,7765 mmol), *terc*-butil-dimetil-tribusilestannilmetoxi-silano (1,8 g, 1,1648 mmol) y tetraquis(trifenilfosfina)paladio(0) (0,3209 g, 0,2777 mmol) en 1,4-dioxano (2,8 ml) se calentó (por irradiación con microondas) a 150°C durante 2 horas. La solución resultante se dejó enfriara temperatura ambiente y se añadió fluoro potásico acuoso saturado (10 ml) seguido de agitación durante 30 minutos. Después, la mezcla se extrajo con acetato de etilo (3 x 25 ml) y los extractos orgánicos combinados (sulfato de magnesio anhidro), se filtraron y se concentraron al vacío para producir el producto bruto en forma de un aceite amarillo.

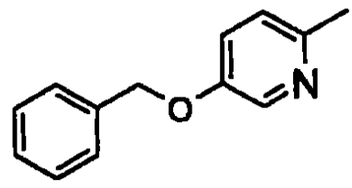
A una solución del residuo bruto en tetrahidrofurano seco (24 ml) se le añadió fluoruro de tetrabutilamonio (3,1 ml de una solución 1,0 M en tetrahidrofurano). La mezcla resultante se agitó a temperatura ambiente durante 16 horas y se concentró a presión reducida. El residuo se purificó por cromatografía en columna ultrarrápida (acetato de etilo al 50%/hexanos a metanol al 10%/acetato de etilo) para producir el alcohol puro (0,6137 g, 71%

en dos etapas) en forma de un sólido blanco.

EMBR (*m/z*): 312 $(M+H)^+$.

Preparación c-53

5-Benciloxi-2-metil-piridina



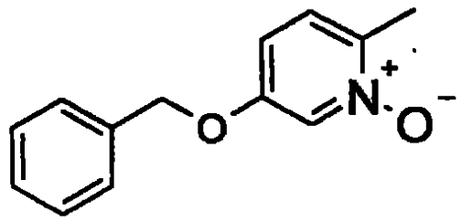
A una solución de 5-hidroxi-2-metilpiridina (20 g, 183,2677 mmol) e hidróxido sódico (8,0638 g, 201,5944 mmol) en acetona (400 ml) y agua (120 ml) se añadió bromuro de bencilo (24 ml, 201, 5944 mmol). La mezcla resultante se calentó a reflujo durante 16 horas y se dejó enfriar a temperatura ambiente. La acetona se retiró al vacío y la mezcla se extrajo con acetato de etilo (3 x 150 ml). Los extractos orgánicos combinados se lavaron con cloruro sódico acuoso saturado (200 ml), se secaron (sulfato de magnesio anhidro), se filtraron y se concentraron al vacío para producir el producto puro (31,35 g, 86%) en forma de un aceite naranja.

EMBR (*m/z*): 200 $(M+H)^+$.

^{1}H RMN ($CDCl_3$, 300 MHz): 8,25 (1H, d, J = 2,8 Hz), 7,43-7,31 (5H, m), 7,15 (1H, dd, J = 8,5, 2,8 Hz), 7,04 (1H, d, J = 8,5 Hz), 5,06 (2H, s), 2,47 (3H, s).

Preparación c-54

1-Óxido de 5-benciloxi-2-metil-piridina



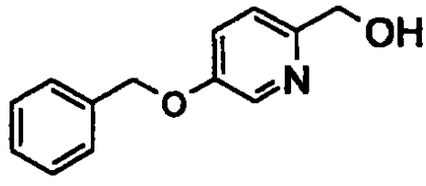
A una solución de 5-benciloxi-2-metil-piridina (31,35 g, 157,34 mmol) en cloroformo seco (800 ml) a temperatura ambiente se le añadió ácido 3-cloroperoxibenzoico (máx. 77%)(38,7888 g, 173,074 mmol). La mezcla resultante se agitó durante 2 horas y después se inactivó con una solución de tiosulfato sódico (36,0805 g, 286,5 mmol) en agua (500 ml) y se agitó durante 15 minutos. Las fases se separaron y la capa orgánica se lavó con agua (500 ml) y cloruro sódico saturado (500 ml), se secó (sulfato de magnesio anhidro), se filtró y se concentró al vacío para producir el producto bruto. El residuo se recristalizó en acetona/hexanos para producir el producto bruto. El residuo se recristalizó en acetona/hexanos para producir el producto puro (33,1597 g, 97%) en forma de un sólido blanco.

EMBR (*m/z*): 216 $(M+H)^+$.

^{1}H RMN ($CDCl_3$, 300 MHz): 8,10-8,09 (1H, m a), 7,38-7,34 (5H, m), 7,10 (1H, d, J = 8,7 Hz), 6,87 (1H, dd, J = 8,7, 2,3 Hz), 5,04 (2H, s), 2,43 (3H, s).

Preparación c-55

(5-Benciloxi-piridin-2-il)-metanol



Una solución de 1-óxido de 5-benciloxi-2-metil-piridina (0,92 g, 4,2741

mmol) en anhídrido acético (6,5 ml) se calentó a 100°C durante 30 minutos. Después de enfriar a temperatura ambiente, la mezcla de reacción se vertió en acetato de etilo (50 ml), se lavó con bicarbonato sódico acuoso saturado (50 ml) y cloruro sódico acuoso saturado (50 ml), se secó (sulfato de magnesio anhidro), se filtró y se concentró al vacío para producir el acetato bruto.

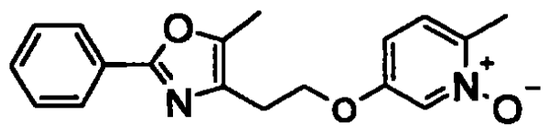
Al residuo bruto en metanol (45 ml) se le añadió carbonato potásico (2,1784 g, 15,7719 mmol) y la solución se dejó en agitación a temperatura ambiente durante 16 horas. La mezcla de reacción se vertió en agua (50 ml) y los extractos orgánicos se retiraron a presión reducida. El residuo resultante se extrajo con acetato de etilo (3 x 50 ml) y los extractos orgánicos combinados se secaron (sulfato de magnesio anhidro), se filtraron y se concentraron al vacío para producir el producto bruto. El residuo se purificó por cromatografía en columna ultrarrápida (hexanos a metanol al 20%/acetato de etilo) para producir el alcohol puro (0,5719 g, 62% para las dos etapas) en forma de un sólido blanco.

EMBR (*m/z*): 216 $(M+H)^+$.

^{1}H RMN ($CDCl_3$, 300 MHz): 8,31 (1H, d, *J* = 2,8 Hz), 7,44-7,31 (5H, m), 7,27 (1H, dd, *J* = 8,7, 2,8 Hz), 7,17 (1H, d, *J* = 8,5 Hz), 5,11 (2H, s), 4,69 (2H, s).

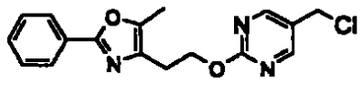
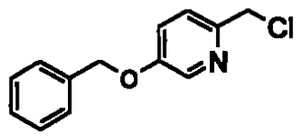
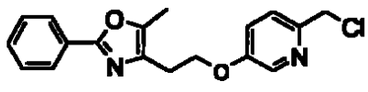
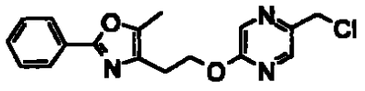
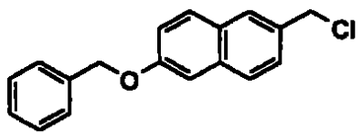
Preparación c-56

1-Óxido de 2-metil-5-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-piridina



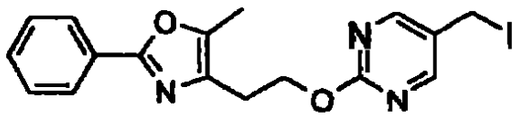
A una solución de 2-metil-5-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-piridina (6,7973 g, 23,0917 mmol) en cloroformo seco (140 ml) a temperatura ambiente

se le añadió ácido 3-cloroperoxibenzoico (máx. 77%) (7,7629 g, 34,6376 mmol). La mezcla resultante se agitó durante 2 horas y después se inactivó con una solución de tiosulfato sódico (4,3621 g, 34,6376 mmol) en agua (25 ml) y se agitó durante 15 minutos. Las fases se separaron y la capa orgánica se lavó con agua (50 ml) y cloruro sódico saturado (50 ml), se secó (sulfato de magnesio anhidro), se filtró y se concentró al vacío para producir el producto bruto. El aceite amarillo pálido (7,0689 g, 98%) se usó sin purificación adicional.

Prep Nº	Estructura	^{1}H RMN	EM (*m/z*) (BR o AR)
c-59			para BR 330 $(M+H)^+$
c-60			para BR 234 $(M+H)^+$
c-61			para BR 329 $(M+H)^+$
c-62		($CDCl_3$, 300 MHz) 8,16 (2H, s), 7,97 (2H, d, *J* = 7,7 Hz), 7,40 (3H, s), 4,61 (4H, m), 2,99 (2H, t, *J* = 6,7 Hz), 2,35 (3H, s)	para BR 330 $(M+H)^+$
c-63		($CDCl_3$, 400 MHz) 7,75-7,72 (3H, m), 7,50-7,33 (6H, m), 7,24-7,22 (2H, m), 5,18 (2H, s), 4,74 (2H, s)	para BR 282 $(M+H)^+$

Preparación c-84

5-(Yodometil)-2-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridina

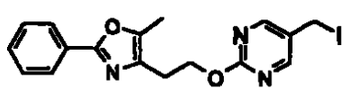
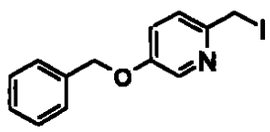
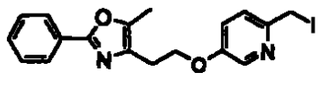
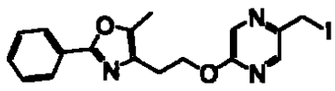
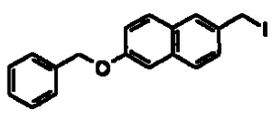


Se añadió yoduro sódico (0,750 g) a una solución de 5-(clorometil)-2-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridina (Preparación 27)(0,690 g, 2,10 mmol) en acetona (5 ml) y la mezcla se calentó a reflujo durante 30 minutos, se enfrió y se evaporó. El residuo se suspendió en acetato de etilo y se filtró a través de una capa de gel de sílice. El filtrado se evaporó para dar el compuesto del título en forma de un sólido cristalino amarillo que se usó directamente en las siguientes reacciones.

EMBR (*m/z*): 421 $(M+H)^+$.

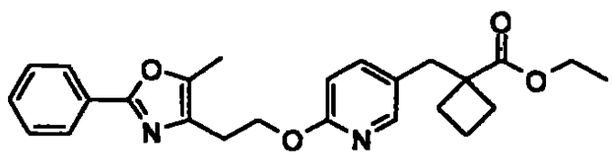
Preparaciones c-65 a c-69

Las Preparaciones c-65 a c-69 se prepararon por el procedimiento general de la Preparación c-64

Prep Nº	Estructura	^{1}H RMN	EM (*m/z*) (BR o AR)
c-65			para BR 422 $(M+H)^+$
c-66			para BR 326 $(M+H)^+$
c-67			para BR 421 $(M+H)^+$
c-68			para BR 422 $(M+H)^+$
c-69		($CDCl_3$, 400 MHz) 7,76-7,66 (3H, m), 7,49-7,32 (6H, m), 7,24-7,18 (2H, m), 5,18 (2H, s), 4,63 (2H, s)	para BR 375 $(M+H)^+$

Preparación c-70

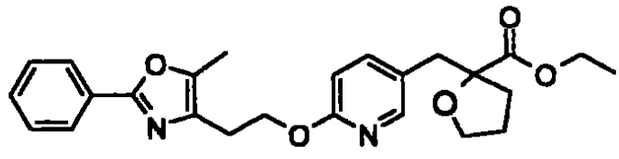
1-({6-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridin-3-il}metil)ciclobutano carboxilato de etilo



Se añadió gota a gota (bis)trimetilsilil amiduro sódico (3,0 ml de una solución 1 M en tetrahidrofurano, 3,0 mmol) a una solución de ciclobutanoato de etilo (0,41 ml, 3,0 mmol) en tetrahidrofurano anhidro (5 ml) a -60°C. La mezcla se agitó durante 1 hora y después se añadió gota a gota una solución de 5-(yodometil)-2-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridina (Preparación 28) (0,271 g, 0,64 mmol) en tetrahidrofurano anhidro (4 ml). La mezcla resultante se agitó a -60°C durante 1 hora y después se inactivó con cloruro amónico acuoso saturado y se calentó a temperatura ambiente. La mezcla se extrajo con acetato de etilo y la fase orgánica se secó (sulfato de magnesio anhidro), se filtró y se evaporó para producir una mezcla 1:1 del compuesto del título y un dímero (0,160 g) que se usó directamente en la siguiente etapa.
EMBR (*m/z*): 421 $(M+H)^+$.

Preparación c-71

2-({6-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridin-3-il}metil)tetrahidrofuran-2-carboxilato de etilo



Se añadió gota a gota (bis)trimetilsilil amiduro sódico (3,18 ml de una solución 1 M en tetrahidrofurano, 3,18 mmol) a una solución de 2-tetrahidrofuranoato de etilo (0,458 g, 3,18 mmol) en tetrahidrofurano anhidro (4

ml) a -50°C. La mezcla se agitó durante 45 minutos y después se añadió gota a gota una solución de 5-(yodometil)-2-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridina (Preparación 28)(0,267 g, 0,64 mmol) en tetrahidrofurano anhidro (2 ml). La mezcla resultante se agitó a -50°C durante 1,5 horas y después se inactivó con cloruro amónico acuoso saturado y se calentó a temperatura ambiente. La mezcla se extrajo con acetato de etilo y la fase orgánica se secó (sulfato de magnesio anhidro), se filtró y se evaporó. El residuo se purificó por cromatografía en columna ultrarrápida (acetato de etilo del 25% al 35%/hexanos) para producir el compuesto del título en forma de un aceite incoloro (0,250 g, 90%).

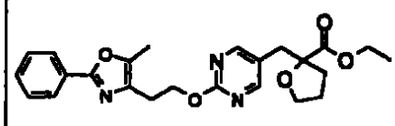
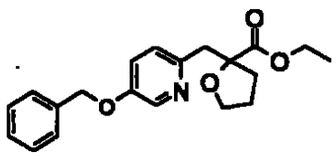
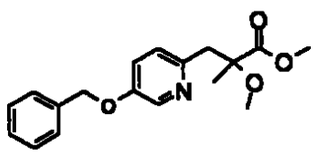
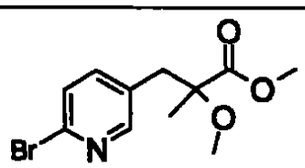
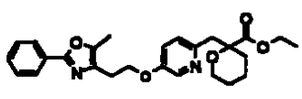
EMBR (*m/z*): 437 $(M+H)^+$.

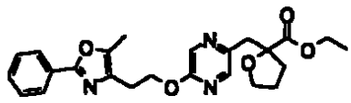
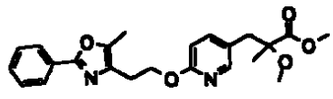
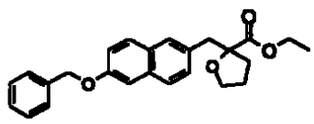
^{1}H RMN ($CDCl_3$, 300 MHz) 7,95 (3H, m), 7,51 (1H, dd, *J* = 2,5, 8,5 Hz), 7,43-7,36 (3H, m), 6,61 (1H, d, *J* = 8,5 Hz), 4,51 (2H, t, *J* = 6,8 Hz), 4,29.4,18 (1H, m), 4,13 (2H, c, *J* = 7,2 Hz), 3,95-3,82 (2H, m), 3,10 (1H, d, *J* = 14,1 Hz), 2,95 (2H, t, *J* = 6,8 Hz), 2,86 (1H, d, *J* = 14,1 Hz), 2,31 (3H, s), 2,26-2,20 (1H, m), 1,92-1,77 (2H, m), 1,70-1,61 (1H, m), 1,21 (3H, t, *J* = 7,2 Hz).

Preparaciones c-72 a c-79

Las Preparaciones c-72 a c-79 se prepararon por el procedimiento general de la Preparación c-71

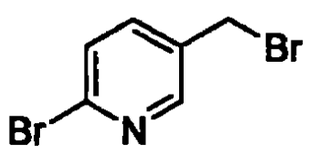
Prep Nº	Estructura	^{1}H RMN	EM (*m/z*) (BR o AR)

c-72		($CDCl_3$, 300 MHz) 8,38 (2H, s), 7,97-7,94 (2H, m), 7,44-7,38 (3H, m), 4,59 (2H, t, *J* = 7,0 Hz), 4,15 (2H, c, *J* = 7,0 Hz), 3,99-3,86 (2H, m), 3,13 (1H, d, *J* = 14,3 Hz), 3,00 (1H, t, *J* = 6,9 Hz), 2,84 (1H, d, *J* = 14,3 Hz), 2,35 (3H, s), 2,26-2,20 (1H, m), 1,91-1,93 (4H, m), 1,23 (3H, t, *J* = 7,0 Hz).	para BR 438 $(M+H)^+$
c-73		($CDCl_3$, 300 MHz) 8,27 (1H, d, *J* = 2,3 Hz), 7,42-7,32 (5H, m), 7,20-7,13 (2H, m), 5,06 (2H, s), 4,13 (2H, c,J = 13,9 Hz), 3,33 (1H, d, *J* = 13,9 Hz), 3,14 (1H, d, *J* = 13,9 Hz), 2,64-2,55 (1H, m), 2,27-2,20 (1H, m), 1,89-1,63 (4H, m), 1,24 (3H, t, *J* = 13,9 Hz).	para BR 342 $(M+H)^+$
c-74		($CDCl_3$, 300 MHz) 8,27 (1H, d, *J* = 2,6 Hz), 7,42-7,29 (5H, m), 7,16 (1H, dd, *J* = 8,7, 2,8 Hz), 7,14-7,08 (1H, m), 5,06 (2H, s), 3,71 (3H, s), 3,30 (3H, s), 3,16 (2H, s), 1,40 (3H, s)	para BR 316 $(M+H)^+$
c-75		($CDCl_3$, 400 MHz) 8,14 (1H, d, *J* = 2,3 Hz), 7,41 (1H, dd, *J* = 8,3, 2,5 Hz), 7,36 (1H, dd, *J* = 8,3, 0,8 Hz), 3,69 (3H, s), 3,27 (3H, s), 2,99 (1H, d, *J* = 13,9 Hz), 2,87 (1H, d, *J* = 13,9 Hz), 1,33 (3H, s)	para BR 289 $(M+H)^+$
c-76		($CDCl_3$, 400 MHz) 8,17 (1H, d, *J* = 2,3 Hz), 7,96 (2H, dd, *J* = 7,7, 1,9 Hz), 7,43-7,38 (3H, m), 7,12 (1H, d, *J* = 8,1 Hz), 7,09 (1H, dd, *J* = 8,6, 2,8 Hz), 4,24 (2H, t, *J* = 6,7 Hz), 4,15 (2H, c, *J* = 7,2 Hz), 3,88-	para BR 451 $(M+H)^+$

		3,84 (1H, m), 3,64 (1H, dt, J = 11,6, 3,3 Hz), 3,07 (2H, s), 2,96 (2H, t, J = 6,6 Hz), 2,36 (3H, s), 2,22-2,18 (1H, m), 1,52-1,36 (5H, m), 1,20 (3H, t, J = 7,1 Hz).	
c-77		($CDCl_3$, 300 MHz) 8,09 (1H, s), 7,91-8,01 (3H, m), 7,34-7,45 (3H, m), 4,48-4,64 (2H, m), 3,84-4,24 (2H, m), 3,22 (1H, d, J = 15,0 Hz), 3,11 (1H, d, J = 15,0 Hz), 2,91-3,03 (1H, m), 2,31-2,35 (1H, m), 1,65-2,30 (2H, m), 1,24 (3H, t, J =6,6 Hz).	para BR 438 $(M+H)^+$
c-78		($CDCl_3$, 300 MHz) 7,96 (1H, m), 7,92 (2H, d, J = 2,1 Hz), 7,41 (4H, m), 6,63 (1H, d, J = 8,5 Hz), 4,52 (2H, t, J = 6,8 Hz), 3,70 (3H, s), 3,30 (3H, m), 2,93 (4H, m), 2,33 (3H, s), 1,33 (3H, s)	para BR 411 $(M+H)^+$
c-79		($CDCl_3$, 400 MHz) 7,69 (1H, d, J = 9,3 Hz), 7,64-7,62 (2H, m), 7,49-7,48 (2H, m), 7,42-7,32 (4H, m), 7,21-7,18 (2H, m), 5,17 (2H, s), 4,24-4,18 (2H, m), 3,96-3,86 (2H, m), 3,33 (1H, d, J = 13,6 Hz), 3,13 (1H, d, J = 13,8 Hz), 2,32-2,20 (1H, m), 2,03-1,89 (3H, m), 1,19 (3H, t, J = 7,1 Hz).	para BR 391 $(M+H)^+$

<u>Preparación c-80</u>

<u>2-bromo-5-(bromometil)piridina</u>



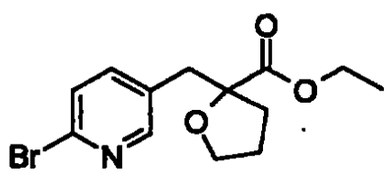
Se añadió cuidadosamente tribromuro de fósforo (100 mmol, 27,1 g, 2,0 equiv.) a 2-cloro-5-hidroximetil piridina (50,0 mmol, 7,18 g, 1,0 equiv.). La piridina se agrupo conjuntamente y la mezcla se calentó a 160 grados C. Dentro de un periodo de 5 minutos a >150°C, se observó que la mezcla era de un color muy oscuro y que se producía desprendimiento de gas. La mezcla se agitó a esta misma temperatura durante aproximadamente 2,5 horas, momento en el que se enfrió a temperatura ambiente. La mezcla se enfrió adicionalmente a 0°C después de lo cual se añadió bicarbonato sódico muy cuidadosamente (alta exotermia). Según se hacía menos vigorosa la espumación, se añadió hielo a la mezcla hasta que la espumación se redujo. Después se añadió cuidadosamente bicarbonato sódico sólido para conseguir un pH de ~8-9. La mezcla se extrajo con acetato de etilo y la capa orgánica se lavó con salmuera y se secó sobre sulfato de magnesio anhidro. Se concentró al vacío para producir un sólido oscuro. Este material se disolvió en una cantidad mínima de DCM y se purificó usando un Biotage Sp4 65i sobre un gradiente de acetato de etilo al 0-100% en hexanos para producir el compuesto del título en forma de un sólido amarillo pálido (5,57 g, 44%).

EMBR: 252 $(M+H)^+$.

^{1}H RMN /DMSO-d_6, 400 MHz): 8,39 (1H, s), 7,59 (1H, d, J = 8,5 Hz), 7,48 (1H, d, J = 8,5 Hz), 4,46 (2H, s).

Preparación c-81

2-[(6-Bromopiridin-3-il)metil]tetrahidrofuran-2-carboxilato de etilo



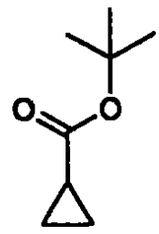
A una solución de tetrahidrofuran-2-carboxilato de etilo (52,9 mmol, 9,10 g, 1,5 equiv.) enfriada a -78°C en THF (90 ml) se le añadió gota a gota una solución de diisopropilamiduro de litio 2 M (52,9 mmol,1,5 equiv.) en una mezcla de heptano/THF/etilbenceno. Se dejó que se formara el enolato durante una hora a la misma temperatura baja, después de lo cual se añadió gota a gota una solución de 2-bromo-5-(bromometil)piridina (35,3 mmol, 8,85 g, 1,0 equiv.) en THF. La reacción se dejó calentar suavemente a temperatura ambiente durante toda la noche. La reacción se interrumpió con cloruro amónico saturado. La mezcla se extrajo con acetato de etilo y el extracto orgánico se lavó con salmuera. La capa orgánica se secó sobre sulfato de magnesio anhidro y se concentró al vacío para producir un aceite amarillo. Este producto bruto se purificó en un Biotage Sp4 65i sobre un gradiente de acetato de etilo del 5% al 95% en hexanos para producir un aceite dorado (8,70 g, 78%).

EMBR: 315 $(M+H)^+$.

^{1}H RMN (DMSO-d_6, 400 MHz); 8,21 (1H, s), 7,40-7,49 (2H, m), 3,94 (2H, c, J = 7,0 Hz), 3,71-3,85(2H, m), 3,05-3,11 (1H, m), 2,91-2,97 (1H, m), 2,38-2,47 (1H, m), 1,83-2,09 (3H, m), 1,09 (3H, t, J = 7,0 Hz).

Preparación c-82

Éster terc-butílico del ácido ciclopropanocarboxílico



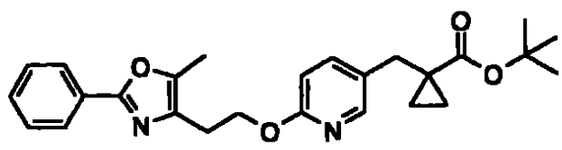
Se añadió ácido sulfúrico concentrado (3,45ml, 62,7832 mmol) a una

suspensión agitada vigorosamente de sulfato de magnesio anhidro (30,1987 g, 251,1326 mmol) en diclorometano (250 ml). La mezcla se agitó durante 15 minutos, tiempo después de lo cual se añadieron ácido ciclopropanocarboxílico (5 ml, 62,7832 mmol) y 2-metil-propan-2-ol (30 ml, 313,9158 mmol). La mezcla se detuvo firmemente y se agitó a temperatura ambiente durante 16 horas. Después, la mezcla de reacción se inactivó con bicarbonato sódico acuoso saturado (450 ml) y se agitó hasta que todo el sulfato de magnesio se había disuelto. Las fases se separaron y la fase orgánica se lavó con agua (100 ml) y cloruro sódico acuoso saturado (100 ml), se secó (sulfato de magnesio anhidro), se filtró y se concentró al vacío para producir el éster puro (8,3921 g, 59,0162 mmol) en forma de un líquido incoloro.

^{1}H RMN ($CDCl_3$, 300 MHz): 1,45 (9H, s), 0,93-0,86 (3H, m), 0,79-0,73 (2H, m).

Preparación c-83

Éster terc-butílico del ácido 1-[6-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-piridin-3-ilmetil]-ciclopropanocarboxílico



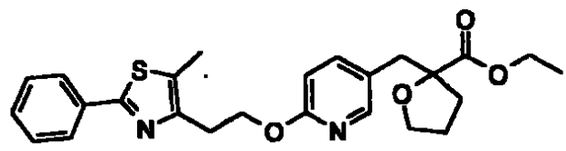
A una solución de diisopropilamina (0,14 ml, 0,9518 mmol) en tetrahidrofurano seco (2,4 ml) a 0°C en una atmósfera de nitrógeno se le añadió butillitio (0,38 ml de una solución 2,5 M en hexanos, 0,9518 mmol). La solución resultante se agitó durante 30 minutos y después se enfrió a -50°C. A esto se le añadió una solución de éster terc-butílico del ácido ciclopropanocarboxílico (0,1269 g, 0,8924 mmol) en tetrahidrofurano seco (1 ml) y se continuó agitando durante 2 horas. Después se añadió gota a gota una

solución de 5-yodometil-2-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-piridina (0,25g, 0,5949 mmol) en tetrahidrofurano seco (1 ml) y la solución se agitó durante 3 horas más. La reacción se inactivó por la adición de cloruro amónico acuoso saturado (25 ml) y se extrajo con acetato de etilo (3 x 25 ml). Los extractos orgánicos combinados después se secaron (sulfato de magnesio anhidro), se filtraron y se concentraron al vacío para producir el producto bruto y el yoduro de partida restante. El residuo se purificó por cromatografía en columna ultrarrápida (hexanos a acetato de etilo al 60%/hexanos) para producir el éster (0,0827 g, 32%) parcialmente contaminado con el yoduro de partida, en forma de un sólido amarillo pálido.

EMBR (*m/z*): 435 $(M+H)^+$.

Preparación c-84

2-({6-[2-(5-metil-2-fenil-1,3-tiazol-4-il)etoxi]piridin-3-il}metil)tetrahidrofuran-2-carboxilato de etilo

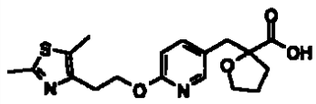
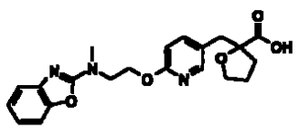
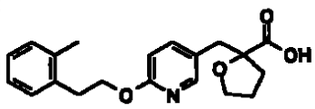
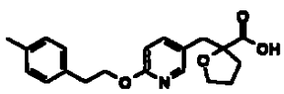


A una solución purgada con argón de la bromopiridina (0,636 mmol) en tolueno (12 ml) se le añadió acetato de paladio (II) (11,4 mg, 0,0508 mmol) y 2-(di-t-butilfosfino)-1,1'-binaftilo racémico (25,4 mg, 0,0636 mmol). Se dejó que se formara el complejo activado durante aproximadamente diez minutos, momento en el que se añadieron carbonato de cesio (414 mg, 1,27 mmol) y el alcohol apropiado (0,956 mmol). La mezcla se calentó a 115ºC y se agitó a esta temperatura durante 12-18 horas. La mezcla se enfrió a temperatura ambiente y se filtró a través de una capa de sílice. La capa de filtro se lavó con 2-3

alícuotas de acetato de etilo y los filtrados orgánicos se combinaron y se concentraron al vacío. El residuo resultante se purificó por cromatografía ultrarrápida o se usó sin purificación adicional.

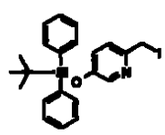
Preparaciones c-85 a c-88

Las Preparaciones c-85 a c-88 se prepararon por procedimientos análogos a los usados para la Preparación c-84

Prep Nº	Estructura	^{1}H RMN	EM (*m/z*) (BR o AR)
c-85		(DMSO-d_6, 400 MHz)	para BR 420 $(M+H)^+$
c-86			
c-87			
c-88			

Preparación c-89

5-{[*terc*-butil(difenil)silil]oxi}-2-(yodometil)piridina



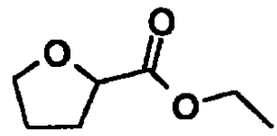
A una solución de 2-bromometil-5-(*terc*-butil-difenil-silaniloxi)-piridina

(Schow, S.R.; Quinn DeJoy, S.; Wick, M.M.; Kerwar, S.S. *J. Org. Chem*, **1994**, *59*, 6850-6852) (1.2692 g, 2.9763 mmol) en acetona (15 ml) se le añadió yoduro sódico (0,8922 g, 5,9526 mmol) y la mezcla heterogénea resultante se agitó durante 3 horas a temperatura ambiente. La mezcla de reacción se concentró al vacío y el residuo resultante se diluyó con acetato de etilo (50 ml) y se lavó con agua (50 ml). La capa orgánica se lavó adicionalmente con bicarbonato sódico acuoso saturado (50 ml) y tiosulfato sódico acuoso saturado (50ml). Las capas acuosas combinadas se extrajeron con acetato de etilo (3 x 50 ml) y los extractos orgánicos combinados se secaron (sulfato de magnesio anhidro), se filtraron y se concentraron al vacío para producir el producto bruto. El residuo se purificó por cromatografía en columna ultrarrápida (hexanos a acetato de etilo al 20%/hexanos) para producir un aceite amarillo pálido (0,72 g, 51%). Este compuesto fue inestable a la hora de su concentración , de forma que se usó inmediatamente.

EMBR (*m/z*): 474 $(M+H)^+$.

Preparación c-90

Tetrahidrofuran-2-carboxilato de etilo



A una solución de ácido tetrahidrofuran-2-carboxílico (20 g, 172,2356 mmol) en etanol anhidro (100 ml) se le añadió ácido sulfúrico concentrado (0,46 ml). La mezcla resultante se agitó a reflujo durante 16 horas y después se dejó enfriar a temperatura ambiente. A esto se le añadió agua (100 ml) y se extrajo con éter dietílico (3 x 100 ml). Los extractos orgánicos combinados se lavaron

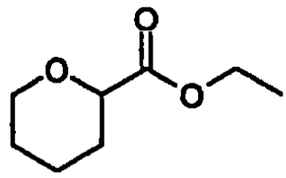
con bicarbonato sódico acuoso saturado (2 x 50 ml) y cloruro sódico acuoso saturado (100 ml), se secaron (sulfato de magnesio anhidro), se filtraron y se concentraron al vacío para producir el producto puro en forma de un líquido incoloro (22,5964 g, 91%).

EMBR (*m/z*): 145 $(M+H)^+$.

^{1}H RMN ($CDCl_3$, 300 MHz) 4,38 (1H, dd, *J* = 4,9, 8,1 Hz), 4,14 (2H, c, *J* = 7,2 Hz), 3,99-3,92 (1H, m), 3,88-3,81 (1H, m), 2,24-2,12 (1H, m), 2,00-1,79 (3H, m), 1,22 (3H, t, *J* = 7,2 Hz).

Preparación c-91

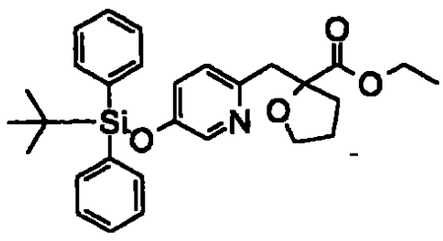
Éster etílico del ácido tetrahidro-piran-2-carboxílico



El compuesto anterior se preparó de acuerdo con el procedimiento descrito en Rychnovsky, S. D.; Hata, T.; Kim, A. I.; Buckmelter, A. J. *Org. Lett* **2001**, *3*, 807-810.

Preparación c-92

2-[(5-{[[*terc*-butil(difenil)silil]oxi}piridin-2-il)metil]tetrahidrofuran-2-carboxilato de etilo



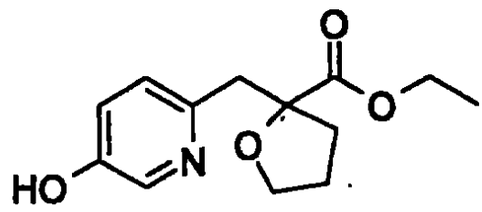
A una solución de tetrahidrofuran-2-carboxilato de etilo (Preparación 32)(1,0965 g, 7,604 mmol) en tetrahidrofurano anhidro (7 ml) a -50°C, en una atmósfera de nitrógeno se le añadió gota a gota bis(trimetilsilil)amiduro sódico (7,6 ml de una solución 1,0 M en tetrahidrofurano, 7,604 mmol). La mezcla de reacción se agitó durante 1 hora y después se añadió gota a gota una solución de 5-(terc-butil-difenil-silaniloxi)-2-yodometil-piridina (Preparación 31) (0,72 g, 1,5208 mmol) en tetrahidrofurano anhidro (7 ml). La solución resultante se agitó a -50°C durante 2 horas y después se inactivó con cloruro amónico acuoso saturado (25 ml). Esto después se extrajo con acetato de etilo (3 X 25 ml), se secó (sulfato de magnesio anhidro), se filtró y se concentró al vacío para producir el producto bruto. El residuo se purificó por cromatografía en columna ultrarrápida (hexanos a acetato de etilo al 40%/hexanos) para producir un aceite incoloro (0,2438 g, 33%).

EMBR (*m/z*): 490 $(M+H)^+$.

^{1}H RMN ($CDCl_3$, 300 MHz) 8,07 (1H, d, *J* = 2,5 Hz), 7,67-7,63 (4H, m), 7,41-7,31 (6H, m), 6,97 (1H, d, *J* = 8,5 Hz), 6,86 (1H, dd, *J* = 2,8, 8,5 Hz), 4,21 (2H, c, *J* = 7,2 Hz), 4,09 (2H, c, *J* = 7,2 Hz), 3,22 (1H, d, *J* = 13,9 Hz), 3,07 (1H, d, *J* = 13,9 Hz), 2,53-2,44 (1H, m), 2,31-2,15 (1H, m), 1,82-1,72 (1H, m), 1,60-1,46 (1H, m), 1,25 (3H, t, *J* = 7,2 Hz), 1,09 (9H, s).

Preparación c-93

2-[(5-Hidroxipiridin-2-il)metil]tetrahidrofuran-2-carboxilato de etilo



A una solución de 2-[(5-[[*terc*-butil(difenil)silil]oxi]piridin-2-il)metil]tetrahidrofuran-2-carboxilato de etilo (Preparación c-92) (0,5118 g, 1,1677 mmol) en tetrahidrofurano anhidro (10 ml) se le añadió gota a gota fluoruro de tetrabutilamonio (1,3 ml de una solución 1,0 M en tetrahidrofurano). La mezcla resultante se agitó a temperatura ambiente durante 1 hora y los volátiles se retiraron al vacío. El residuo se purificó por cromatografía en columna ultrarrápida (acetato de etilo al 50%/hexanos a metanol al 10%/acetato de etilo) para producir un aceite incoloro (0,2321 g, 79%).

EMBR (*m/z*): 252 $(M+H)^+$.

^{1}H RMN ($CDCl_3$, 300 MHz) 8,10 (1H, d, j = 2,3 Hz), 7,20 (1H, d, J = 8,5 Hz), 7,14 (1H, dd, J = 2,6, 8,5 Hz), 4,14 (2H, c, *J* = 7,2 Hz), 3,88 (2H, c, *J* = 7,8 Hz), 3,35 (1H, d, *J* = 13,9 Hz), 3,12 (1H, d, *J* = 13,9 Hz), 2,30-2,21 (1H, m), 2,04-1,94 (1H, m), 1,89-1,76 (1H, m), 1,75-1,63 (1H, m), 1,20 (3H, t, *J* = 7,2 Hz).

Preparación c-93a

Preparación alternativa de 2-[(5-hidroxipiridin-2-il)metil]tetrahidrofuran-2-carboxilato de etilo

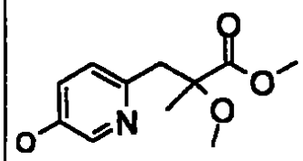
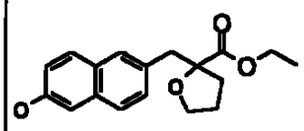
A una solución de éster etílico del ácido 2-(5-benciloxi-piridin-2-ilmetil)-tetrahidro-furan-2-carboxílico (0,6065 g, 1,7765 mmol) en etanol seco (10 ml) se le añadió paladio (0,0607 g, 10% en peso sobre carbono activado). La solución resultante se calentó a 45°C en una atmósfera de hidrógeno durante 16 horas. Después de enfriar a temperatura ambiente, la solución se filtró a través de un lecho de 7,62 cm de Celite y se lavó con etanol (100 ml). Después el filtrado se concentró al vacío para producir el producto bruto que se usó sin purificación adicional.

EMBR (*m/z*): 252 $(M+H)^+$.

^{1}H RMN ($CDCl_3$, 400 MHz): 8,10 (1H, d, J = 2,3 Hz), 7,20 (1H, d, J = 8,5 Hz), 7,14 (1H, dd, J = 2,6, 8,5 Hz), 4,14 (2H, c, J = 7,2 Hz), 3,88 (2H, c, J = 7,8 Hz), 3,35 (1H, d, J = 13,9 Hz), 3,12 (1H, d, J = 13,9 Hz), 2,30-2,21 (1H, m), 2,04-1,94 (1H, m), 1,89-1,76 (1H, m), 1,75-1,63 (1H, m),1,20 (3H, t, J = 7,2 Hz).

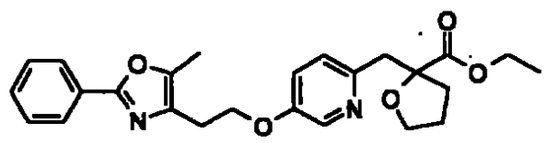
Preparaciones c-94 a c-95

Las Preparaciones c-94 a c-95 se prepararon por el procedimiento general usado para la Preparación c-93

Prep Nº	Estructura	^{1}H RMN	EM (*m/z*) (BR o AR)
c-94		($CDCl_3$, 400 MHz) 8,24 (1H, sa), 7,37-7,30 (1H, ma), 7,24-7,22 (1H, ma), 3,71 (3H, s), 3,28 (3H,s), 3,23-3,18 (2H, m), 1,40 (3H, s)	para BR 226 $(M+H)^+$
c-95		($CDCl_3$, 400 MHz) 7,64 (1H, d, J = 8,6 Hz), 7,61 (1H, s), 7,53 (1H, d, J = 8,6 Hz), 7,36 (1H, dd, J = 1,7, 8,6 Hz), 7,05-7,01 (2H, m), 5,32 (1H, s), 3,99-3,88 (2H, m), 3,34 (1H, d, J = 13,6 Hz), 3,11 (1H, d, J = 13,9 Hz), 2,33-2,27 (1H, m), 2,00-1,93 (1H, m), 1,89-1,77 (1H, m), 1,73-1,65 (1H, m), 1,19 (3H, t, J = 7,3 Hz).	para BR 301 $(M+H)^+$

Preparación c-96

2-({5-[2-(5-Metil-2-fenil-1,3-oxazol-4-il)etoxi]piridin-2-il}metil)tetrahidrofuran-2-carboxilato de etilo



A una solución de 2-[(5-hidroxipiridin-2-il)metil]tetrahidrofuran-2-carboxilato de etilo (Preparación c-93) (0,2321 g, 0,9237 mmol), 2-(5-metil-2-fenil-oxazol-4-il)-etanol (0,2065 g, 1,0161 mmol) y trifenilfosfina (0,3634 g, 1,3856 mmol) en tetrahidrofurano anhidro (10 ml) en una atmósfera de nitrógeno se le añadió gota a gota una solución de azodicarboxilato de dietilo (0,22 ml, 1,3856 mmol) en tetrahidrofurano anhidro (1 ml). La solución resultante se agitó a temperatura ambiente durante 16 horas y los volátiles se retiraron al vacío. Este residuo después se purificó por cromatografía en ultrarrápida columna (hexanos a acetato de etilo al 50%/hexanos) para producir un aceite amarillo pálido (0,2618 g, 65%).

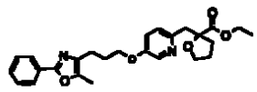
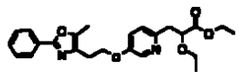
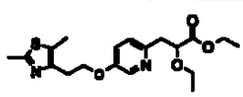
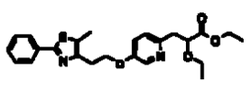
EMBR (*m/z*): 437 $(M+H)^+$.

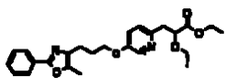
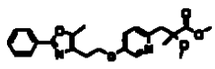
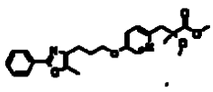
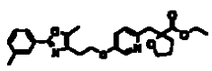
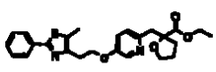
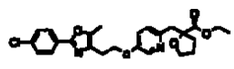
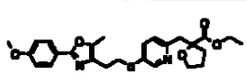
^{1}H RMN ($CDCl_3$, 300 MHz) 8,20 (1H, d, *J* = 2,8 Hz), 7,99 (1H, d, *J* = 2,5 Hz), 7,96 (1H, d, *J* = 1,7 Hz), 7,70-7,64 (1H, m), 7,49-7,39 (2H, m), 7,19 (1H, d, *J* = 8,5 Hz), 7,11 (1H, dd, *J* = 3,0, 8,5 Hz), 4,26 (2H, t, *J* = 6,6 Hz), 4,17 (2H, c, *J* = 7,2 Hz), 3,95-3,81 (2H, m), 3,33(1H, d, *J* = 13,8 Hz), 3,16 (1H, d, *J* = 13,8 Hz), 2,98 (2H, t, *J* = 6,6 Hz), 2,37 (3H, s), 2,34-2,22 (1H, m), 2,09-2,00 (1H, m), 1,87-1,76 (1H, m), 1,72-1,62 (1H, m), 1,23 (3H, t, *J* = 7,2 Hz).

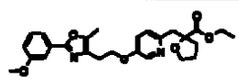
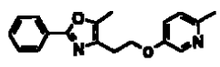
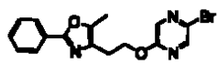
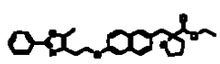
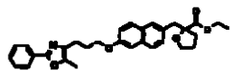
Preparaciones c-97 a c-112

Las Preparaciones c-97 a c-112 se prepararon por el procedimiento general usado para la Preparación c-96

Prep Nº	Estructura	^{1}H RMN	EM (*m/z*)

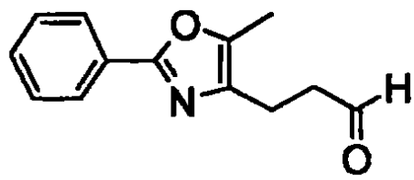
			(BR o AR)
c-97		($CDCl_3$, 300 MHz) 8,19 (1H, d, *J* = 2,8 Hz), 7,97-7,93 (1H, m), 7,42-7,39 (3H, m), 7,18 (1H, d, *J* = 8,5 Hz), 7,10 (1H, dd, *J* = 8,5, 2,8 Hz), 4,16 (2H, c, *J* = 7,2 Hz), 3,98 (2H, t, *J* = 6,0 Hz), 3,92-3,82 (2H, m), 3,33 (1H, d, *J* = 13,8 Hz), 3,14 (1H, d, *J* = 13,9 Hz), 2,67 (2H, t, *J* = 6,0 Hz), 2,26 (3H, s), 2,19-2,10 (2H, m), 1,91-1,63 (4H, m), 1,22 (3H, t, *J* = 7,2 Hz).	para BR 451 $(M+H)^+$
c-98		($CDCl_3$, 400 MHz) 8,20 (1H, dd, *J* = 2,0, 1,5 Hz), 7,95 (2H, dd, *J* = 7,7, 1,9 Hz), 7,43-7,36 (3H, m), 7,10 (2H, d, *J* = 1,5 Hz), 4,25 (2H, t, *J* = 6,6 Hz), 4,23-4,13 (3H, m), 3,63-3,55 (1H, m), 3,37-3,27 (1H, m), 3,15-3,02 (2H, m), 2,97 (2H, t, *J* = 6,7 Hz), 2,35 (3H, s), 1,21 (3H, t, *J* = 7,2 Hz), 1,08 (3H, t, *J* = 7,1 Hz)	para BR 425 $(M+H)^+$
c-99		($CDCl_3$, 400 MHz) 8,19 (1H, dd, *J* = 2,0, 1,5 Hz), 7,08-7,07 (2H, m), 4,26-4,23 (3H, m), 4,16 (2H, c, *J* = 7,0 Hz), 3,63-3,56 (1H, m), 3,36-3,28 (1H, m), 3,15-3,02 (4H, m), 2,58 (3H, s), 2,34 (3H, s), 1,21 (3H, t, *J* = 7,1 Hz), 1,08 (3H, t, *J* = 7,0 Hz)	para BR 379 $(M+H)^+$
c-100		($CDCl_3$, 400 MHz) 8,22 (1H, dd, *J* = 2,4, 1,1 Hz), 7,86-7,83 (2H, m), 7,42-7,36 (3H, m), 7,11-7,10 (2H, m), 4,35 (2H, t, *J* = 6,8 Hz), 4,24 (1H, dd, *J* = 8,3, 5,1 Hz), 4,18 (2H, c, *J* = 7,1 Hz), 3,63-3,56 (1H, m), 3,36-3,28 (1H, m), 3,16 (2H, t, *J* = 6,8 Hz), 3,14 (1H, dd, *J* = 13,9, 5,1 Hz), 3,05 (1H, dd, *J* = 13,9, 8,3 Hz), 2,45 (3H, s), 1,22 (3H, t, *J* = 7,1 Hz), 1,09 (3H, t, *J* = 7,1 Hz)	para BR 441 $(M+H)^+$

c-101		($CDCl_3$, 400 MHz) 8,22 (1H, dd, J = 2,0, 1,5 Hz), 7,97-7,93 (2H, m), 7,43-7,37 (3H, m), 7,11-7,10 (2H, m), 4,25 (1H, dd, J = 8,6, 5,1 Hz), 4,18 (2H, c, J = 7,2 Hz), 3,99 (2H, t, J = 6,2 Hz), 3,64-3,56 (1H, m), 3,37-3,29 (1H, m), 3,14 (1H, dd, J = 13,9, 5,1 Hz), 3,06 (1H, dd, J = 13,9, 8,6 Hz), 2,68 (2H, t, J = 7,1 Hz), 2,26 (3H, s), 2,18-2,12 (2H, m), 1,22 (3H, t, J = 7,1 Hz), 1,09 (3H, t, J = 7,0 Hz)	para BR 439 $(M+H)^+$
c-102		($CDCl_3$, 400 MHz) 8,18 (1H, dd, J = 2,3, 1,3 Hz), 7,96 (2H, dd, J = 7,6, 2,0 Hz), 7,54-7,51 (3H, m), 7,10-7,08 (2H, m), 4,25 (2H, t, J = 6,7 Hz), 3,29 (3H, s), 3,15 (2H, s), 2,96 (2H, t, J = 6,7 Hz), 2,36 (3H, s), 2,32 (3H, s), 1,38 (3H, s)	para BR 411 $(M+H)^+$
c-103		($CDCl_3$, 400 MHz) 8,20 (1H, t, J = 7,8 Hz), 7,97-7,93 (2H, m), 7,44-7,38 (3H, m), 7,09 (2H, d, J = 7,8 Hz), 3,99 (2H, t, J = 6,1 Hz), 3,72 (3H, s), 3,30 (3H, s), 2,68 (2H, t, J = 7,1 Hz), 2,62 (2H, t, J = 6,7 Hz), 2,27 (3H, s), 2,18-2,12 (2H, m), 1,40 (3H, s)	para BR 425 $(M+H)^+$
c-104			para BR 451 $(M+H)^+$
c-105			para BR 453 $(M+H)^+$
c-106			para BR 471 $(M+H)^+$
c-107			para BR 467 $(M+H)^+$

c-108			para BR 467· $(M+H)^+$
c-109		($CDCl_3$, 300 MHz) 8,16 (1H, d, *J* = 2,6 Hz), 7,97-7,94 (2H, m), 7,48-7,39 (3H, m), 7,10 (1H, dd, *J* = 8,7, 3,0 Hz), 7,02 (1H, d, *J* = 8,5 Hz), 4,25 (2H, t, *J* = 6,7 Hz), 2,98 (2H, t, *J* = 6,7 Hz), 2,48 (3H, s), 2,36 (3H, s)	para BR 295 $(M+H)^+$
c-110		($CDCl_3$, 300 MHz) 8,16 (1H, d, *J* = 1,3 Hz), 7,96 (3H, dd, *J* = 7,4, 1,7 Hz), 7,41 (3H, dd, *J* = 5,3, 1,9 Hz), 4,58 (2H, t, *J* = 6,7 Hz), 2,98 (2H, t, *J* = 6,8 Hz), 2,34 (3H, s)	para BR 360 $(M)^-$
c-111		($CDCl_3$, 400 MHz) 7,99-7,97 (2H, m), 7,66 (1H, d, *J* = 8,8 Hz), 7,62-7,59 (2H, m), 7,45-7,35 (4H, m), 7,12-7,08 (2H, m), 4,35 (2H, t, *J* = 6,8 Hz), 4,16-4,09 (2H, m), 3,96-3,85 (2H, m), 3,32 (1H, d, *J* = 13,6 Hz), 3,11 (1H, d, *J* = 13,9 Hz), 3,04 (2H, t, *J* = 6,8 Hz), 2,40 (3H, s), 2,31-2,24 (1H, m), 1,99-1,76 (1H, m), 1,69-1,60 (1H, m), 1,18 (3H, t, *J* = 7,1 Hz)	para BR 486 $(M+H)^+$
c-112		($CDCl_3$, 400 MHz) 7,99-7,97 (2H, m), 7,67 (1H, d, *J* = 8,8 Hz), 7,61-7,59 (2H, m), 7,45-7,35 (4H, m), 7,12 (1H, dd, *J* = 2,3, 8,8 Hz), 7,08-7,07 (1H, d, *J* = 2,3 Hz), 4,16-4,06 (4H, m), 3,96-3,86 (2H, m), 3,33 (1H, d, *J* = 13,6 Hz), 3,11 (1H, d, *J* = 13,6 Hz), 2,74 (2H, t, *J* = 7,1 Hz), 2,32-2,18 (6H, m), 1,99-1,91 (1H, m), 1,86-1,77 (1H, m), 1,69-1,61 (1H, m), 1,19 (3H, t, *J* = 7,1 Hz)	para BR 500 $(M+H)^+$

Preparación c-113

3-(5-Metil-2-fenil-oxazol-4-il)-propionaldehído



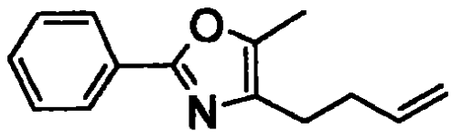
A una solución de 3-(5-metil-2-fenil-oxazol-4-il)-propan-1-ol (1,0 g, 4,6026 mmol) en diclorometano (20 ml) se le añadió clorocromato de piridinio (9,9213 g de ~20% en peso sobre SiO_2, 9,2051 mmol). La mezcla resultante se agitó en una atmósfera de nitrógeno a temperatura ambiente durante 16 horas y los volátiles se retiraron a presión reducida. El residuo se purificó por cromatografía en columna ultrarrápida (hexanos a acetato de etilo) para producir el aldehído puro (0,4752 g, 48%) en forma de un aceite incoloro.

EMBR (*m/z*): 216 (M+H)+.

^{1}H RMN ($CDCl_3$, 300 MHz): 9,84 (1H, s), 7,96-7,93 (2H, m), 7,42-7,37 (3H, m), 2,85 (2H, dd, *J* = 6,0, 9,0 Hz), 2,80 (2H, d, *J* = 6,0 Hz), 2,33 (3H, s).

Preparación c-114

4-But-3-enil-5-metil-2-fenil-oxazol



A una solución de yoduro de metil trifenilfosfonio (1,7848 g, 4,41543 mmol) en tetrahidrofurano seco (95 ml) en una atmósfera de nitrógeno a 0ºC se le añadió gota a gota butillitio (1,8 ml de una solución 2,5 M en hexanos, 4,4154 mmol).La suspensión se disolvió y la solución se volvió naranja. Después de 10 minutos, se añadió gota a gota una solución de 3-(5-metil-2-fenil-oxazol-4-il)-propionaldehído (0,4752 g, 2,2077 mmol) en tetrahidrofurano seco (15 ml) y la

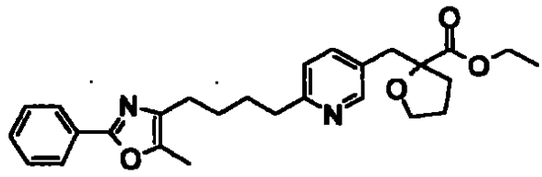
solución se dejó calentar a temperatura ambiente. Después de 16 horas, se añadieron hexanos (200 ml) y el precipitado se retiró por filtración. El filtrado después se extrajo con agua (200 ml) y la fase orgánica se secó (sulfato de magnesio anhidro), se filtró y se concentró al vacío para producir el producto bruto. El residuo se purificó por cromatografía en columna ultrarrápida (hexanos a acetato de etilo) para producir el compuesto del título puro (0,291 g, 62%) en forma de un aceite incoloro.

EMBR (*m/z*): 214 $(M+H)^+$.

^{1}H RMN ($CDCl_3$, 300 MHz): 7,99-7,96 (2H, m), 7,43-7,38 (3H, m), 5,93-5,79 (1H, m), 5,09-5,02 (1H, m), 5,00-4,95 (1H, m), 2,57 (2H, t, *J* = 7,4 Hz), 2,42 (2H, t, *J* = 7,4 Hz), 2,31 (3H, s).

Preparación c-115

Éster etílico del ácido 2-[6-[4-(5-metil-2-fenil-oxazol-4-il)-butil]-piridin-3-ilmetil]tetrahidro-furan-2-carboxílico



Se añadió 9-borabiciclononano (5,5 ml de una solución 0,5 M en tetrahidrofurano, 2,729 mmol) a una solución amarilla de 4-but-3-enil-5-metil-2-fenil-oxazol (0,291 g, 1,3645 mmol) en tetrahidrofurano seco (1,3 ml). La mezcla se agitó a temperatura ambiente durante 4 horas y después se transfirió a otro matraz que contenía éster etílico del ácido 2-(6-bromo-piridin-3-ilmetil)-tetrahidro-furan-2-carboxílico (0,3297 g, 1,0496 mmol), dicloruro de paladio bis(difenilfosfino)ferroceno (0,0857 g, 0,1050 mmol), carbonato de cesio (0,9551 g, 2,9389 mmol), trifenilarsina (0,0322 g, 0,1050 mmol) en *N,N*-

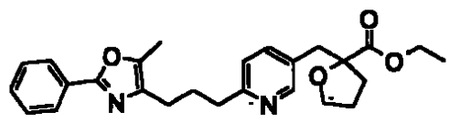
dimetilformamida (2,8 ml) y agua (0,23 ml). La mezcla de color rojo oscuro se agitó durante 16 horas a temperatura ambiente en una atmósfera de nitrógeno. Después de enfriar a 0°C, la reacción se inactivó con acetato sódico acuoso 2 M (5 ml) y peróxido de hidrógeno acuoso al 30% (2 ml). La solución resultante se agitó durante 2 horas, se diluyó con agua (25 ml) y se extrajo con acetato de etilo (4 x 50 ml). Los extractos orgánicos combinados se lavaron con agua (25 ml), se secaron (sulfato de magnesio anhidro), se filtraron y se concentraron al vacío para dar el producto bruto. El residuo se purificó por cromatografía en columna ultrarrápida (hexanos a acetato de etilo) para producir el compuesto del título (0,2805 g, 60%) en forma de un aceite amarillo pálido.

EMBR (*m/z*): 449 $(M+H)^+$.

^{1}H RMN ($CDCl_3$, 300 MHz): 8,34 (1H, d, *J* = 1,9 Hz), 7,95 (2H, dd, *J* = 7,7, 1,9 Hz), 7,52 (1H, dd, *J* = 8,0, 2,2 Hz), 7,42-7,36 (3H, m), 7,04 (1H, d, *J* = 7,9 Hz), 4,13 (2H, c, *J* = 7,2 Hz), 3,96-3,84 (2H, m), 3,16 (1H, d, *J* = 13,9 Hz), 2,90 (1H, d, *J* = 13,9 Hz), 2,77 (2H, t, *J* = 7,3 Hz), 2,50 (2H, t, *J* = 6,9 Hz), 2,31-2,19 (1H, m), 2,28 (3H, s), 1,92-1,64 (7H, m), 1,20 (3H, t, *J* = 7,2 Hz).

Preparación c-116

Éster etílico del ácido 2-{6-[3-(5-metil-2-fenil-oxazol-4-il)-propil]-piridin-3-ilmetil}-tetrahidro-furan-2-carboxílico



Se añadió 9-borabiciclononano (4,2 ml de una solución 0,5 M en tetrahidrofurano, 2,07 mmol) a una solución amarilla de 4-alil-5-metil-2-fenil-

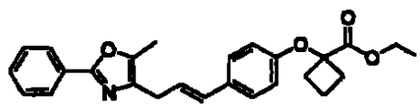
oxazol (0,21g, 1,04 mmol) en tetrahidrofurano seco (1 ml). La mezcla se agitó a temperatura ambiente durante 4 horas y después se transfirió a otro mátraz que contenía éster etílico del ácido 2-(6-bromo-piridin-3-ilmetil)-tetrahidro-furan-2-carboxílico (0,25 g, 0,80 mmol), dicloruro de paladio bis(difenilfosfino)ferroceno (0,07 g, 0,1 mmol), carbonato de cesio (0,72 g, 2,90 mmol), trifenilarsina (0,02 g, 0,1 mmol) en *N,N*-dimetilformamida:agua (4:1, 2,63 ml). La mezcla de color rojo oscuro se agitó durante 16 horas a temperatura ambiente en una atmósfera de nitrógeno. Después de enfriar a 0ºC, la reacción se inactivó con acetato sódico acuoso 2 M (4,7 ml) y peróxido de hidrógeno acuoso al 30% (1,7 ml). La solución resultante se agitó durante 2 horas, se diluyó con agua (20 ml) y se extrajo con acetato de etilo (4 x 50 ml). Los extractos orgánicos combinados se lavaron con agua (20 ml), se secaron (sulfato de magnesio anhidro), se filtraron y se concentraron al vacío para dar el producto bruto. El residuo se purificó por cromatografía en columna ultrarrápida (acetato de etilo al 40%-90%/hexanos) para producir el compuesto del título (0,20 g, 57%) en forma de un aceite incoloro.

EMBR (*m/z*): 435 $(M+H)^+$.

^{1}H RMN (dimetil sulfóxido-d_6, 400 MHz): 8,35 (1H, s), 7,96 (2H, d, *J* = 7,9 Hz), 7,55 (1H, d, *J* = 8,3 Hz), 7,39 (3H, t, *J* = 5,9 Hz), 7,09 (1H, d, *J* = 8,1 Hz), 3,91 (2H, m), 3,80 (2H, t, *J* = 10,9 Hz), 3,17 (1H, d, *J* = 14,0 Hz), 2,91 (1H, d, *J* = 13,94 Hz), 2,81 (2H, t), 2,53 (2H, t, *J* = 7,3 Hz), 2,28 (3H, s), 2,09 (2H, d, *J* = 7,5 Hz), 1,87 (4H, d, *J* = 10,9 Hz), 1,23 (3H, m).

Preparación c-117

1-[4-[(1*E*)-3-(5-metil-2-fenil-1,3-oxazol-4-il)prop-1-en-1-il]fenoxi]ciclobutanocarboxilato de etilo



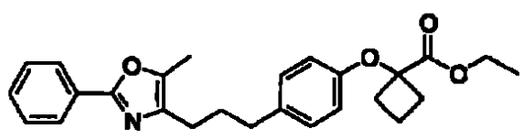
Una mezcla de $Pd(OAc)_2$ (12 mg, 0,05 mmol) y Ph_3P (26 mg, 0,05 mmol) en tolueno (2 ml) se agitó en una atmósfera de nitrógeno a temperatura ambiente durante 1 hora y se continuó por la adición de Et_3N (2 ml) y una solución de 4-alil-5-metil-2-fenil-1,3-oxazol (100 mg, 0,50 mmol) y 1-(4-yodofenoxi)ciclobutanocarboxilato de etilo (173 mg, 0,50 mmol) en tolueno (2 ml). La solución de reacción resultante se calentó a 80ºC en una atmósfera de nitrógeno durante 17 horas y se enfrió a temperatura ambiente. Después de la retirada del disolvente, el residuo se repartió entre EtOAc y salmuera. La fase orgánica separada se lavó con salmuera, se secó sobre Na_2SO_4 y se concentró para dar el producto bruto en forma de un aceite pardo. La purificación por cromatografía en columna de gel de sílice con EtOAc al 20% en hexano dio 85 mg (41%) de un aceite amarillo.

^1H RMN (400 MHz, $CDCl_3$) 1,19 (t, 3H), 1,98 (m, 2H), 2,38 (s, 3H), 2,43 (m, 2H), 2,72 (m, 2H), 3,41 (d, 2H), 4,18 (c, 2H), 6,20 (td, 1H), 6,40 (d, 1H), 6,60 (d, 2H); 7,25 (d, 2H), 7,40 (d, 3H), 8,00 (d, 2H).

EMBR (*m/z*): 418 $(M+H)^+$.

Preparación c-118

1-[4-[3-(5-Metil-2-fenil-1,3-oxazol-4-il)propil]fenoxi]ciclobutanocarboxilato de etilo



Se disolvió 1-[4-[(1*E*)-3-(5-metil-2-fenil-1,3-oxazol-4-il)prop-1-en-1-

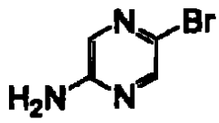
il]fenoxi}ciclobutanocarboxilato de etilo (85 mg, 0,20 mmol) en MeOH(5 ml) y se continuó por la adición de Pd al 10%/C (15 mg). La mezcla se agitó a temperatura ambiente durante 16 horas con un globo, lleno de gas hidrógeno, unido al matraz. La mezcla se filtró a través de una capa de Celite y la torta se aclaró con MeOH. El filtrado se concentró para dar 85 mg (100%) de un aceite amarillo.

^{1}H RMN (400 MHz, $CDCl_3$): 1,19 (t, 3H), 1,92-2,02 (m, 4H), 2,27 (s, 3H), 2,39-2,51 (m, 4H), 2,60 (t, 2H), 2,66-2,77 (m, 2H), 4,19 (c, 2H), 6,60 (d, 2H), 7,05 (d, 2H), 7,36-7,47 (m, 3H), 7,98 (dd, 2H).

EMBR (*m/z*): 420 $(M+H)^+$.

Preparación c-119

5-Bromo-pirazin-2-ilamina



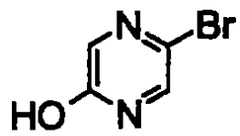
A una solución de pirazin-2-ilamina (2,0 g, 21,03 mmol) en diclorometano seco (120 ml) a 0ºC se le añadió *N*-bromosuccinimida (3,74 g, 21,03 mmol) lentamente para mantener la temperatura interna por debajo de 0ºC. La mezcla se agitó a la misma temperatura durante 24 horas y después se lavó con bicarbonato sódico acuoso saturado (30 ml) y agua (30 ml). Los extractos acuosos combinados se extrajeron con diclorometano (3 x 100 ml). Los extractos orgánicos combinados se secaron (sulfato de magnesio anhidro), se filtraron y se concentraron al vacío para producir el producto bruto. El residuo se purificó por cromatografía en columna ultrarrápida (acetato de etilo del 10% al 50%/hexanos) para producir el compuesto del título (2,57 g, 70%) en forma de un sólido amarillo.

EMBR (*m/z*): 174 (M)$^+$.

^{1} RMN ($CDCl_3$, 300 MHz): 8,08 (1H, d, *J* = 1,3 Hz), 7,76 (1H, d, *J* = 1,3 Hz).

Preparación c-120

5-Bromo-pirazin-2-ol

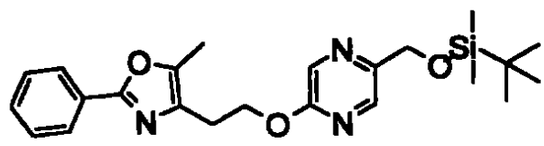


Se añadió por porciones nitrito sódico (1,35 g, 19,53 mmol) a ácido sulfúrico concentrado (9,8 ml) a 0°C. La mezcla se calentó a 50°C hasta que todo el nitrito sódico se había disuelto y la mezcla se enfrió de nuevo a 0°C. Se añadió gota a gota una solución de 5-bromo-pirazin-2-ilamina (2,57 g, 14,68 mmol) en ácido sulfúrico concentrado (14,7 ml) a la solución de nitronio a 0°C. El baño de hielo se retiró, la mezcla se calentó a temperatura ambiente y se agitó durante 15 minutos antes de calentarla a 45°C durante siete minutos. Después de enfriar a temperatura ambiente, la mezcla se vertió lentamente con precaución en agua enfriada con hielo picado (100 ml). La fase acuosa se neutralizó a pH 4 con hidróxido sódico acuoso al 20% y después se extrajo con acetato de etilo (3 x 100 ml). Los extractos orgánicos combinados se lavaron con agua (50 ml), se secaron (sulfato de magnesio anhidro), se filtraron y se evaporaron para producir el compuesto del título (1,88 g, 73%) en forma de un sólido amarillo.

^{1}H RMN ($CDCl_3$, 300 MHz): 8,07 (1H, s), 7,62 (1H, d, *J* = 3,0 Hz).

Preparación c-121

2-(*terc*-butil-dimetil-silaniloximetil)-5-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]pirazina



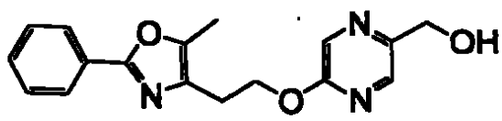
A una solución de 2-bromo-5-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-pirazina (0,50 g, 1,39 mmol) y *terc*-butil-dimetil-tributilestannilmetoxi-silano (0,91 g, 2,09 mmol) en 1,4-dioxano seco (8 ml) se le añadió tetraquistrifenilfosfina(0) paladio (0,16 g, 0,14 mmol).La mezcla se desgasificó tres veces y después se calentó a 120ºC durante 22 horas. Después de enfriar a temperatura ambiente, la mezcla se diluyó con éter dietílico (10 ml) y después se inactivó con fluoruro potásico acuoso saturado (5 ml). La mezcla resultante se agitó durante 30 minutos y después se extrajo con acetato de etilo (3 x 50 ml). La fase orgánica se lavó con agua (30 ml), se secó (sulfato de magnesio anhidro), se filtró y se evaporó para producir el compuesto del título sin purificación adicional.

EMBR (*m/z*): 426 $(M+H)^+$.

^{1}H RMN ($CDCl_3$, 300 MHz): 8,20 (1H, s), 8,09 (1H, s), 7,97 (2H, d, *J* = 7,4 Hz), 7,41 (3H, d, *J* = 5,3 Hz), 4,78 (2H, s), 4,58 (2H, d, *J* = 6,6 Hz), 2,98 (2H, s), 2,34 (3H, s); 0,97 (2H, m), 0,14 (6H, m).

Preparación c-122

{5-[2-(5-Metil-2-fenil-oxazol-4-il)-etoxi]-pirazin-2-il}-metanol



Se añadió gota a gota fluoruro de tetrabutilamonio (2,8 ml de una solución 1 M en tetrahidrofurano, 2,78 mmol) a una solución de 2-(terc-butil-dimetil-silaniloximetil)-5-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-pirazina (~1,39

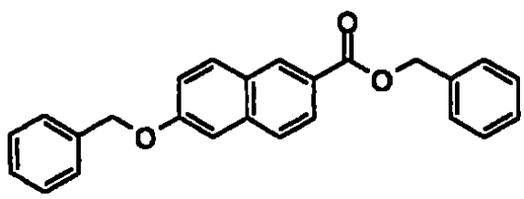
mmol) en tetrahidrofurano seco (20 ml). La mezcla se agitó a temperatura ambiente durante 16 horas y después se inactivó con agua (1 ml) y se acidificó a pH 5 con una solución acuosa 1 M de ácido acético. Los extractos orgánicos se retiraron al vacío y la fase acuosa se extrajo con diclorometano (3 x 50 ml). Los extractos orgánicos combinados se secaron (sulfato de magnesio anhidro), se filtraron y se concentraron al vacío para producir el compuesto del título (0,0928 g, 21%).

EMBR (*m/z*): 312 $(M+H)^+$.

^{1}H RMN ($CDCl_3$, 300 MHz): 8,12 (2H, s), 8,05 (2H, d, *J* = 6,0 Hz), 7,40 (3H, d, *J* = 6,0 Hz), 4,72 (2H, s), 4,59 (2H, t, *J* = 6,0 Hz), 2,99 (2H, t, *J* = 6,0 Hz), 2,33 (3H, s).

Preparación c-123

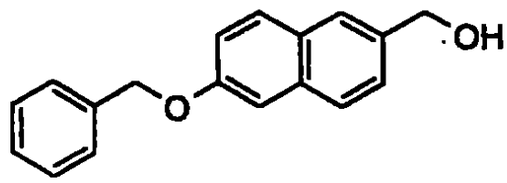
Éster bencílico del ácido 6-benciloxi-naftaleno-2-carboxílico



El compuesto anterior se preparó de acuerdo con el procedimiento descrito en Inui, S.; Suzuki, T.; Limura, N.; Iwane, H.; Nohira, H. *Mol. Cryst. Liq. Cryst. Sci. Technol. Sect. A.* 1994, *239*, 1-10.

Preparación c-124

(6-Benciloxi-naftalen-2-il)-metanol



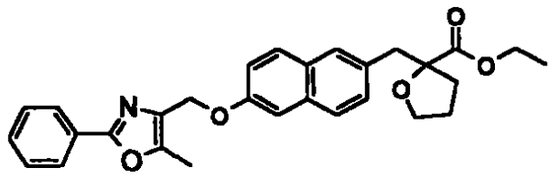
A una solución de éster bencílico del ácido 6-benciloxi-naftaleno-2-carboxílico (7,09 g, 19,24 mmol) en tetrahidrofurano seco (60 ml) en una atmósfera de nitrógeno a 0°C se le añadió hidruro de diisobutilaluminio (58 ml de una solución 1,0 M en tetrahidrofurano, 57,73 mmol). La mezcla resultante se dejó calentar a temperatura ambiente y se agitó durante 16 horas. Se añadió gota a gota una solución de ácido cítrico (19 g) en agua (40 ml) (PRECAUCIÓN: Muy exotérmica). La capa acuosa después se extrajo con acetato de etilo (3 x 50 ml) y los extractos orgánicos combinados se lavaron con cloruro sódico acuoso saturado (50 ml), se secaron (sulfato de magnesio anhidro) y se concentraron al vacío para producir el producto bruto. El residuo se purificó por cromatografía en columna ultrarrápida (hexanos a acetato de etilo) para producir el compuesto del título (4,37 g, 86%) en forma de un sólido blanco.

EMBR (*m/z*): 287 $(M+Na)^+$.

^1H RMN ($CDCl_3$, 400 MHz): 7,76-7,72 (3H, m), 7,50-7,33 (6H, m), 7,25-7,23 (2H, m), 5,18 (2H, s), 4,82 (2H, d, J = 6,1 Hz).

Preparación c-125

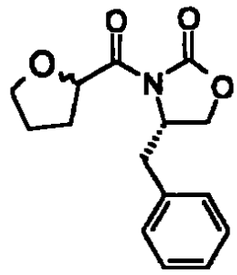
Éster etílico del ácido 2-[6-(5-metil-2-fenil-oxazol-4-ilmetoxi)-naftalen-2-ilmetil]-tetrahidro-furan-2-carboxílico



Una mezcla heterogénea de 2-fenil-4-(clorometil)-5-metiloxazol (0,133 g, 0,639 mmol), éster etílico del ácido 2-(6-hidroxi-naftalen-2-ilmetil)-tetrahidro-furan-2-carboxílico (0,192 g, 0,639 mmol) y carbonato de cesio (0,521 g, 1,59 mmol) en acetonitrilo seco (2 ml) se calentó (en un microondas) a 140°C durante 10 minutos. Se añadió una segunda porción de 2-fenil-4-(clorometil)-5-metiloxazol (0,5 equiv.) y la mezcla se calentó a 200°C durante 20 minutos más. La mezcla de reacción se filtró a través de Celite y se lavó con acetonitrilo (200 ml). El filtrado se concentró al vacío y el residuo se purificó por cromatografía en columna ultrarrápida (hexanos a acetato de etilo) para producir el compuesto del título (0,180 g, 60%) en forma de un aceite incoloro.

Preparación c-126

(4S)-4-Bencil-3-(tetrahidrofuran-2-ilcarbonil)-1,3-oxazolidin-2-ona

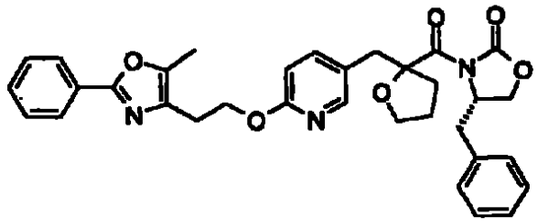


Se añadió gota a gota n-butillitio (22,6 ml de una solución 2,5 M en hexanos, 56,4 mmol) a una solución de (4*S*)-4-bencil-1,3-oxazolidin-2-ona (10,0 g, 56,4 mmol) en tetrahidrofurano (200 ml) a -78°C. La mezcla se agitó durante 30 minutos y después se añadió una solución de cloruro de tetrahidrofuran-2-

carbonilo (9,12 g, 67,7 mmol) en tetrahidrofurano (25 ml). La mezcla se agitó a -78°C durante 30 minutos, se calentó a 0°C durante 1 hora y se inactivó con una solución saturada de cloruro amónico. La mezcla se extrajo con acetato de etilo y la fase orgánica se lavó con salmuera, se secó sobre sulfato de magnesio, se filtró y se evaporó. El residuo se purificó por cromatografía en columna ultrarrápida (1:3 y después 1:2 de acetato de etilo:hexanos) para producir el compuesto del título como una mezcla aproximadamente 1:1 de diastereoisómeros en forma de un aceite incoloro (15,0 g, 97%).

Preparación c-127

(4S)-4-Bencil-3-[[2-({6-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridin-3-il}metil)tetrahidrofuran-2-il]carbonil]-1,3-oxazolidin-2-ona



Se añadió gota a gota (bis)trimetilsilil amiduro sódico (3,57 ml de una solución 1 M en tetrahidrofurano, 3,57 mmol) a una solución de (4S)-4-bencil-3-(tetrahidrofuran-2-ilcarbonil)-1,3-oxazolidin-2-ona (0,983 g, 3,57 mmol) en tetrahidrofurano anhidro (6 ml) a -50°C . La mezcla se agitó durante 45 minutos y después se añadió gota a gota una solución de 5-(yodometil)-2-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridina (Preparación 28) (0,500 g, 1,19 mmol) en tetrahidrofurano anhidro (6 ml). La mezcla resultante se agitó a -50°C durante 1,5 horas, después se inactivó con cloruro amónico acuoso saturado y se calentó a temperatura ambiente. La mezcla se extrajo con acetato de etilo y la fase orgánica se secó (sulfato de magnesio anhidro), se filtró y se evaporó. El

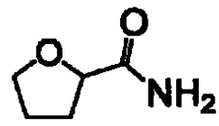
residuo se purificó por cromatografía en columna ultrarrápida (1:1 de acetato de etilo:hexanos) para producir el compuesto del título en forma de un único diastereoisómero en forma de un aceite incoloro (0,617 g, 90%).

EMBR (*m/z*): 568 $(M+H)^+$.

^{1}H RMN ($CDCl_3$, 300 MHz) 8,01 (1H, s), 7,96 (2H, m), 7,61 (1H, dd, *J* = 2,5, 8,5 Hz), 7,40 (3H, m), 7,28 (3H, m), 7,17 (1H, m), 6,64 (1H, d, *J* = 8,6 Hz), 4,55 (3H, m), 4,18 (2H, m), 3,90 (1H, m), 3,79 (1H, m), 3,27 (1H, d, *J* = 14 Hz), 3,20 (1H, m), 3,13 (1H, d, *J* = 14 Hz), 2,96 (2H, t, *J* = 6,8 Hz), 2,79 (1H, m), 2,32 (3H, s), 2,34 (3H, m), 2,11 (1H, m), 1,73 (1H, m), 1,54 (1H, m).

Preparación c-128

Amida del ácido tetrahidro-furan-2-carboxílico



A una solución de ácido tetrahidro-furan-2-carboxílico (2,42 g, 20,82 mmol) en tetrahidrofurano anhidro (120 ml) en una atmósfera de nitrógeno a 0°C se le añadió trietilamina (8,5 ml, 61,23 mmol) y cloroformiato de etilo (2,4 ml, 25,10 mmol). Se formó un precipitado blanco después de la adición de cloroformiato de etilo y la mezcla resultante se agitó durante 45 minutos a 0°C. Se burbujeó gas amoniaco en la solución durante 2 horas y la fuente de gas se retiró. La mezcla de reacción se dejó calentar a temperatura ambiente y se agitó durante 16 horas. La solución se ajustó a pH 1 por la adición de ácido clorhídrico 1 N y después se extrajo con acetato de etilo (3 x 50 ml). Los extractos orgánicos combinados se secaron (sulfato de magnesio anhidro), se filtraron y se concentraron al vacío para dar el producto bruto. El residuo se

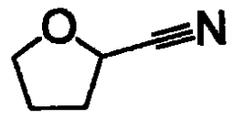
purificó por cromatografía en columna ultrarrápida (hexanos a acetato de etilo al 10%/hexanos) para producir el compuesto del título (0,97 g, 41%) en forma de un sólido blanco.

EMBR (*m/z*): 116 $(M+H)^+$.

^1H RMN ($CDCl_3$, 300 MHz): 4,35 (1H, dd, J = 8,5, 5,8 Hz), 3,92 (2H, m), 2,18 (2H, m), 1,90 (2H, m).

Preparación c-129

Tetrahidro-furan-2-carbonitrilo

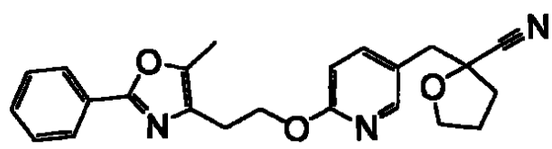


Se añadió lentamente anhídrido trifluoroacético (1,55 g, 7,38 mmol), con una velocidad de una gota cada 120 segundos, a una solución enfriada con hielo (0°C) de amida del ácido tetrahidro-furan-2-carboxílico (0,77 g, 6,71 mmol) y piridina (1,06 g, 13,42 mmol) en 1,4-dioxano anhidro (10 ml). La adición de anhídrido trifluoroacético se controló para mantener la temperatura interna por debajo de 5°C y se completó después de 20 minutos. La mezcla resultante se dejó calentar a temperatura ambiente y se agitó durante 3 horas. Se añadió cloroformo (100 ml) a la mezcla y después se extrajo con agua (30 ml) y cloruro sódico acuoso saturado (20 ml). Los extractos orgánicos se secaron (sulfato de magnesio anhidro), se filtraron y se concentraron al vacío para dar el producto bruto. El residuo se purificó por cromatografía en columna ultrarrápida (hexanos a acetato de etilo al 25%/hexanos) para producir el compuesto del título (0,51 g, 62%) en forma de un aceite incoloro.

^1H RMN ($CDCl_3$, 300 MHz): 4,70 (1H, m), 3,96 (2H, m), 2,24 (2H, m), 2,08 (2H, m).

Preparación c-130

2-[6-[2-(5-Metil-2-fenil-oxazol-4-il)-etoxi]-piridin-3-ilmetil}-tetrahidro-furan-2-carbonitrilo



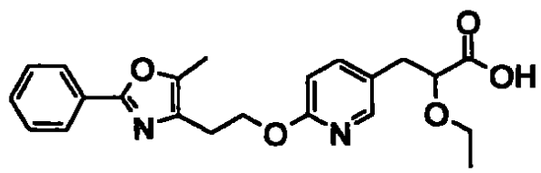
Se añadió bis(trimetilsilil)amiduro sódico (1,8 ml, 1,79 mmol) a una solución de tetrahidro-furan-2-carbonitrilo (0,17 g, 1,79 · mmol) en tetrahidrofurano anhidro (6 ml) en una atmósfera de nitrógeno a -78ºC. La solución amarilla resultante se agitó durante 50 minutos y después se añadió a la solución de enolato una solución de 5-yodometil-2-[2-(5-metil-2-fenil-oxazol-4-il)-etoxi]-piridina (0,25 g, 0,596 mmol) en tetrahidrofurano anhidro (3 ml). La mezcla se agitó a -78ºC durante 1,5 horas y se inactivó con cloruro amónico acuoso saturado (5 ml). La fase acuosa se extrajo con acetato de etilo (3 x 50 ml) y los extractos orgánicos combinados se lavaron con agua (30 ml), se secaron (sulfato de magnesio anhidro), se filtraron y se concentraron a vacio para dar el producto bruto. El residuo se purificó por cromatografía en columna ultrarrápida (acetato de etilo del 7% al 45%/hexanos) para producir el compuesto del título (0,11 g, 46%) en forma de un sólido blanco.

EMBR (*m/z*): 390 $(M+H)^+$.

^{1}H RMN ($CDCl_3$, 300 MHz): 8,03 (1H, d, *J* = 2,5 Hz), 7,96 (2H, m), 7,56 (1H, dd, *J* = 8,5, 2,5 Hz), 7,40 (3H, m), 6,68 (1H, d, *J* = 8,5 Hz), 4,54 (2H, m), 3,96 (2H, m), 3,00 (4H, m), 2,33 (5H, d, *J* = 3,2 Hz), 1,92 (2H, m).

Ejemplo D-1

Ácido 2-etoxi-3-{6-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridin-3-il}propanoico



Se añadió hidróxido de litio monohidrato (180 mg, 4,31 mmol) a una solución de 2-etoxi-3-{6-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridin-3-il}propanoato de etilo (183 mg, 0,431 mmol) en una mezcla de tetrahidrofurano:metanol:agua (1:1:1, 6 ml). La mezcla se agitó durante 18 horas y después los componentes volátiles se retiraron por evaporación. La fase acuosa se acidificó con ácido clorhídrico 3 M y se extrajo con acetato de etilo. La fase orgánica se lavó con salmuera, se secó sobre sulfato de magnesio, se filtró y se evaporó. El residuo se purificó dos veces por cromatografía en columna ultrarrápida (98:2 de diclorometano:metanol) para producir el compuesto del título en forma de un vidrio incoloro (31 mg).

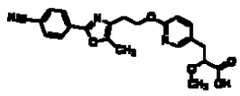
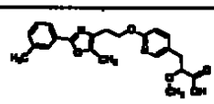
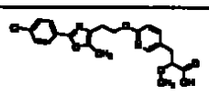
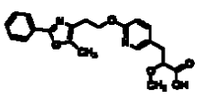
EMBR (*m/z*): 396 $(M)^+$.

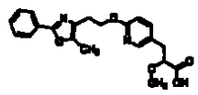
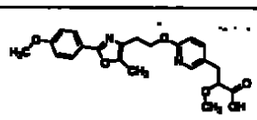
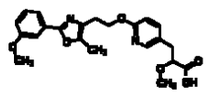
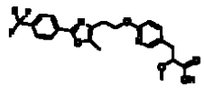
^{1}H RMN ($CDCl_3$, 300 MHz) 7,99 (3H, m), 7,50 (1H, m), 7,40 (3H, m), 6,65 (1H, m), 4,50 (2H, t, J = 7 Hz), 4,01 (1H, m), 3,64 (1H, m), 3,42 (1H, m), 2,98 (4H, m), 2,34 (3H, s), 1,16 (3H, t, *J* = 7 Hz).

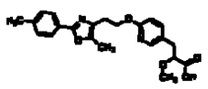
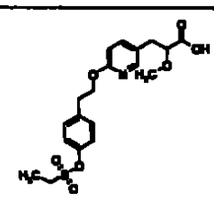
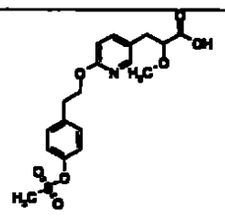
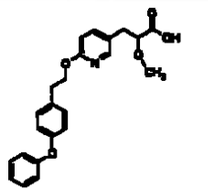
Ejemplos D-2 a D-45

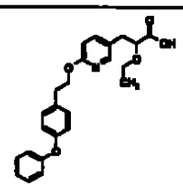
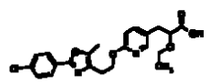
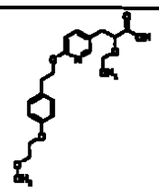
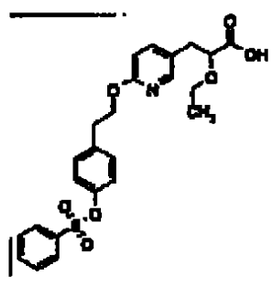
Los Ejemplos D-2 a D-45 se prepararon por procedimientos análogos a los usados para el Ejemplo D-1 por agitación de una solución del éster con hidróxido sódico o de litio en metanol acuoso, etanol acuoso, tetrahidrofurano acuoso o mezclas de los mismos a temperaturas comprendidas entre 20°C y 75°C.

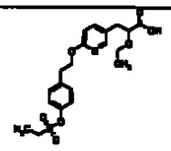
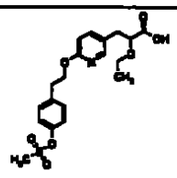
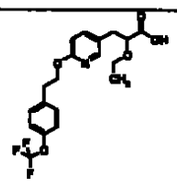
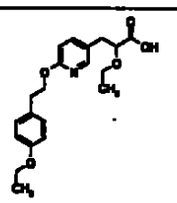
Ej. Nº	Estructura	^{1}H RMN	EM (*m/z*) BR/AR	Análisis

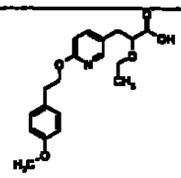
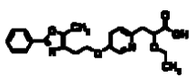
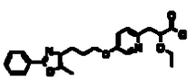
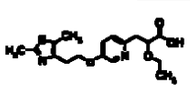
D-2		^{1}H RMN (DMSO-d_6, 400 MHz): 8,05 (2H, d, *J* = 8,6 Hz), 7,98-7,94 (3H, m), 7,55 (1H, dd, *J* = 8,3 y 2,3 Hz), 6,70 (1H, d, *J* = 8,3 Hz), 4,45 (2H, t, *J* = 6,6 Hz), 3,89 (1H, dd, *J* = 7,6 y 5,1 Hz), 3,22 (3H, s), 2,95-2,87 (3H, m), 2,80 (1H, dd, *J* = 14,2 y 7,8 Hz), 2,35 (3H, s)	para BR 408 $(M+H)^+$	
D-3		^{1}H RMN (DMSO-d_6, 400 MHz): 7,98 (1H, d, *J* = 2,3 Hz), 7,73 (1H, s), 7,69 (1H, d, *J* = 7,8 Hz), 7,55 (1H, dd, *J* = 8,6 y 2,3 Hz), 7,37 (1H, t, *J* = 7, 8 Hz), 7,28 (1H, d, *J* = 7,1 Hz), 6,70 (1H, d, 8,3 Hz), 4,44 (2H, t, *J* = 6,6 Hz), 3,89 (1H, dd, *J* = 8,1 y 4,8 Hz), 3,22 (3H, s), 2,92-2,88 (3H, m), 2,80 (1H, d, *J* = 14,7 y 8,1 Hz), 2,36 (3H, s), 2,31 (3H, s)	Calculado para $C_{22}H_{23}N_3O_5$ 397,1758. Encontrado: 397,1775	Calculado para $C_{22}H_{24}N_3O_5.0.5H_2O$ C 65,17 H 6,22 N 6,91. Encontrado: C 65,03 H 6,10 N 7,07
D-4		^{1}H RMN (DMSO-d_6, 400 MHz): 7,98 (1H, d, *J* = 1,8 Hz), 7,92 (2H, d, *J* = 8,6 Hz), 7,58-7,55 (3H, m), 6,72 (1H, d, *J* = 8,6 Hz), 4,46 (2H, t, *J* = 6,6 Hz), 3,91 (1H, dd, *J* = 7,8 y 4,6 Hz), 3,24 (3H, s), 2,94-2,89 (3H, m), 2,82 (1H, dd, *J* = 14,4 y 7,6 Hz), 2,33 (3H, s).	Calculado para $C_{21}H_{22}ClN_3O_5$ 417,1212. Encontrado: 417,1232	
D-5		^{1}H RMN (DMSO-d_6, 400 MHz): 12,71 (1H, s), 7,98 (1H, d, *J* = 2,3 Hz), 7,90 (2H, dd, *J* = 7,6 y 2,0 Hz), 7,55 (1H, dd, *J* = 8,6 y 2,3 Hz), 7,51-7,46 (3H, m), 6,71 (1H, d, *J* = 8,6 Hz), 4,44 (2H, t, *J* = 6,6 Hz), 3,89 (1H, dd, *J* = 7,6 y 5,1 Hz), 3,22 (3H, s), 2,92-2,88 (3H, m), 2,80 (1H, dd, *J* = 14,2 y 7,6 Hz), 2,32 (3H, s).		Calculado para $C_{21}H_{23}N_3O_5.0.1H_2O$ C 65,65 H 5,82 N 7,29. Encontrado: C 65,45 H 5,92 N 7,26.

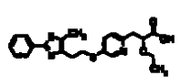
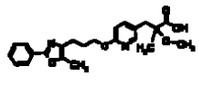
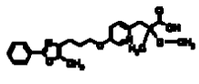
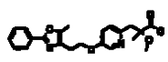
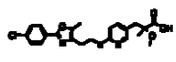
D-6		^{1}H RMN (DMSO-d_6, 400 MHz): 12,81 (1H, s), 7,96 (1H, d, *J* = 2,0 Hz), 7,90 (2H, dd, *J* = 7,7 y 1,9 Hz), 7,55 (1H, dd, *J* = 8,6 y 2,3 Hz), 7,51-7,46 (3H, m), 6,70 (1H, d, *J* = 8,6 Hz), 4,44 (2H, t, *J* = 6,8 Hz), 3,88 (1H, dd, *J* = 7,6 y 4,8 Hz), 3,22 (3H, s), 2,92-2,87 (3H, m), 2,80 (1H, dd, *J* = 14,2 y 7,8 Hz), 2,32 (3H, s).		Calculado para $C_{21}H_{22}N_2O_6$0. 25$H_2$0 C 65,19 H 5,86 N 7,24. Encontrado: C 65,19 H 5,80 N 7,03
D-7		^{1}H RMN (DMSO-d_6, 400 MHz): 12,54 (1H, s), 7,96 (1H, d, *J* = 2,0 Hz), 7,83 (2H, d, *J* = 9,1 Hz), 7,55 (1H, dd, *J* = 8,6 y 2,3 Hz), 7,03 (2H, d, *J* = 8,8 Hz), 6,70 (1H, d, *J* = 8,6 Hz), 4,43 (2H, t, *J* = 6,8 Hz), 3,90 (1H, dd, *J* = 7,8 y 4,6 Hz), 3,80(3H, s), 3,22 (3H, s), 2,92-2,86 (3H, m), 2,80 (1H, dd, *J* = 14,7 y 7,6 Hz), 2,29 (3H, s).	Calculado para $C_{22}H_{23}N_2O_6$ 413,1707. Encontrado: 413,1717	
D-8		^{1}H RMN (DMSO-d_6, 400 MHz): 12,77 (1H, s), 7,96 (1H, d, *J* = 2,3 Hz), 7,55 (1H, dd, *J* = 8,3 y 2,3 Hz), 7,48 (1H, d, *J* = 7,8 Hz), 7,41 (1H, d, *J* = 8,1 Hz), 7,39-7,37 (1H, m), 7,04 (1H, dd, *J* = 8,1 y 2,5 Hz), 6,71 (1H, d, *J* = 8,6 Hz), 4,44 (2H, t, *J* = 6,8 Hz), 3,89 (1H, dd, *J* = 7,8 y 4,8 Hz), 3,81 (3H, s), 3,22 (3H, s), 2,92-2,86 (3H, m), 2,80 (1H, dd, *J* = 14,4 y 8,0 Hz), 2,31 (3H, s).	Calculado para $C_{22}H_{23}N_2O_6$ 413,1707. Encontrado: 413,1715	
D-9		^{1}H RMN (DMSO-d_6, 400 MHz): 12,70 (1H, s), 8,04 (2H, d, *J* = 8,1 Hz), 7,91 (1H, d, *J* = 2,0), 7,80 (2H, d, *J* = 8,3 Hz), 7,49 (1H, dd, *J* = 8,3 y 2,4 Hz), 6,85 (1H, d, *J* = 8,3 Hz), 4,40 (2H, t, *J* = 6,6 Hz), 3,84 (1H, dd, *J* = 7, y 4,7 Hz), 3,16 (3H, s), 2,90-2,82 (3H, m), 2,74 (1H, dd, *J* = 14,4 y 7,8	Calculado para $C_{22}H_{22}F_3N_2O_6$ 451,1478. Encontrado: 451,1474	

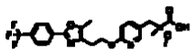
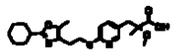
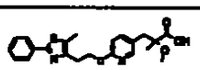
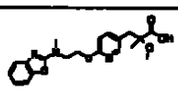
		Hz), 2,29 (3H, s).		
D-10		^{1}H RMN (DMSO-d_6, 400 MHz): 12,76 (1H, s), 7,96 (1H, d, *J* = 2,3 Hz), 7,79 (2H, d, *J* = 8,1), 7,55 (1H, dd, *J* = 8,6 y 2,5 Hz), 7,29 (2H, d, *J* = 8,1 Hz), 6,68 (1H, d, *J* = 8,3 Hz), 4,43 (2H, t, *J* = 6,8 Hz), 3,89 (1H, dd, *J* = 7,8 y 4,8 Hz), 3,22 (3H, s), 2,92-2,87 (3H, m), 2,80 (1H, dd, *J* = 14,2 y 7,8 Hz), 2,34 (3H, s), 2,30 (3H, s).	Calculado para $C_{22}H_{23}N_3O_5$ 397,1758. Encontrado: 397,1770	Calculado para $C_{22}H_{23}N_3O_5$0. 3$H_2$0 C 65,75 H 6,17 N 6,97. Encontrado: C 65,74 H 6,14 N 6,81
D-11		^{1}H RMN (MeOH-d_4, 400 MHz): 8,30 (1H, s), 7,58 (1H, d, *J* = 9,2 Hz), 7,11 (2H, d, *J* = 8,2 Hz), 6,71 (2H, d, *J* = 8,2 Hz), 6,31 (1H, d, *J* = 9,2 Hz), 4,57 (2H, t, *J* = 6,5 Hz), 4,18 (1H, dd, *J* = 13,5, 0,2 Hz), 3,98 (2H, c, *J* = 7,7 Hz), 3,52 (3H, s), 3,28 (2H, t, *J* = 6,5 Hz), 3,05-3,11 (1H, m), 2,89-2,96 (1H, m), 1,44 (3H, t, *J* = 7,7 Hz)	EMBR: 410 $(M+H)^+$	
D-12		^{1}H RMN (MeOH-d_4, 400 MHz): 8,30 (1H, s), 7,58 (1H, d, *J* = 9,2 Hz), 7,10 (2H, d, *J* = 8,2 Hz), 6,74 (2H, d, *J* = 8,2 Hz), 6,31 (1H, d, *J* = 9,2 Hz), 4,57 (2H, t, *J* = 6,5 Hz), 4,18 (1H, dd, *J* = 13,5, 0,2 Hz), 3,52 (3H, s), 3,34 (3H, s), 3,28 (2H, t, *J* = 6,5 Hz), 3,06-3,11 (1H, m), 2,89-2,96 (1H, m)	para BR 396 $(M+H)^+$	
D-13		^{1}H RMN (MeOH-d_4, 400 MHz): 8,30 (1H, s), 7,58 (1H, d, *J* = 9,2 Hz), 7,31-7,37 (2H, m, *J* = 8,0, 7,5, 0,2, 0,2 Hz), 7,06-7,14 (3H, m), 6,96-7,04 (4H, m), 6,31 (1H, d, *J* = 9,2 Hz), 4,57 (2H, t, *J* = 6,5 Hz), 4,18 (1H, dd, *J* = 13,5, 0,2 Hz), 3,52 (3H, s), 3,28 (2H, t, *J* = 6,5 Hz), 3,06-3,11 (1H, m), 2,89-2,97 (1H, m)	para BR 394 $(M+H)^+$	

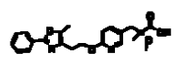
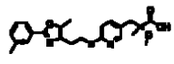
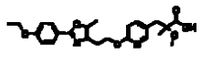
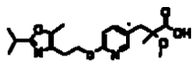
D-14		^{1}H RMN (MeOH-d_4, 400 MHz): 8,28-8,34 (1H, m), 7,59 (1H, m), 7,31-7,37 (2H, m), 6,96-7,14 (7H, m), 6,27-6,34 (1H, m), 4,53-4,60 (2H, m), 4,22-4,30 (1H, m), 3,49-3,66 (2H, m), 3,25-3,31 (2H, m), 3.05-3,11 (1H, m), 2,89-2,97 (1H, m), 1,19 (3H, t, *J* = 7,0 Hz)	EMBR 409 $(M+H)^+$	
D-15		^{1}H RMN (MeOH-d_4, 400 MHz): 8,31 (1H, s), 8,02 (2H, d, *J* = 8,3 Hz), 7,59 (1H, d, *J* = 9,1 Hz), 7,43 (2H, d, *J* = 8,3 Hz), 6,31 (1H, d, *J* = 9,1 Hz) 4,20-4,29 (3H, m) 3,49-3,66 (2H, m), 3,05-3,11 (1H, m), 2,89-2,97 (1H, m) 2,70 (2H, t, *J* = 8,0 Hz), 2,19 (3H, s), 1,19 (3H, t, *J* = 7,0 Hz)	para BR 432 $(M+H)^+$	
D-16		^{1}H RMN (MeOH-d_4, 400 MHz): 8,31 (1H, s), 7,59 (1H, d, *J* = 9,1 Hz), 6,87 (2H, d, *J* = 8,2 Hz), 6,73 (2H, d, *J* = 8,2 Hz), 6,31 (1H, d, *J* = 9,2 Hz) 4,57 (2H, t, *J* = 6,5 Hz), 4,43 (2H, s) 4,26 (1H, dd, *J* = 13,5, 0,2 Hz), 3,76 (2H, s), 3,49-3,66 (2H, m), 3,36 (3H, s), 3,28 (2H, t, *J* = 6,5 Hz), 3,05-3,11 (1H, m), 2,89-2,97 (1H, m), 1,19 (3H, t, *J* = 7,0 Hz)	para BR 391 $(M+H)^+$	
D-17		^{1}H RMN (MeOH-d_4, 400 MHz): 8,31 (1H, s), 7,66-7,74 (5H, m), 7,59 (1H, d, *J* = 9,1 Hz), 7,19 (2H, d, *J* = 8,2 Hz), 6,86 (2H, d, *J* = 8,3 Hz), 6,31 (1H, d, *J* = 9,2 Hz) 4,57 (2H, t, *J* = 6,5 Hz), 4,26 (1H, dd, *J* = 13,5, 0,2 Hz), 3,49-3,66 (2H, m), 3,28 (2H, t, *J* = 6,5 Hz), 3,05-3,11 (1H, m), 2,89-2,97 (1H, m), 1,19 (3H, t, *J* = 7,0 Hz)	para BR 473 $(M+H)^+$	

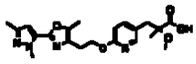
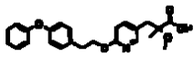
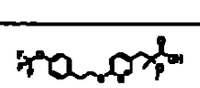
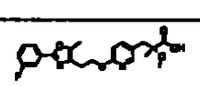
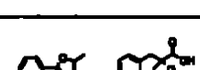
D-18		^{1}H RMN (MeOH-d_4, 400 MHz): 8,31 (1H, s), 7,59 (1H, d, *J* = 9,1 Hz), 7,11 (2H, d, *J* = 8,2 Hz), 6,71 (2H, d, *J* = 8,2 Hz), 6,31 (1H, d, *J* = 9,2 Hz) 4,57 (2H, t, *J* = 6,5 Hz), 4,26 (1H, dd, *J* = 13,5, 0,2 Hz), 3,98 (2H, c, J = 7,7 Hz) 3,49-3,66 (2H, m), 3,28 (2H, t, *J* = 6,5 Hz), 3,05-3,11 (1H, m), 2,89-2,97 (1H, m), 1,44 (3H, t, J = 7,7Hz) 1,19 (3H, t, *J* = 7,0 Hz)	para BR 425 $(M+H)^+$	
D-19		^{1}H RMN (MeOH-d_4, 400 MHz): 8,31 (1H, s), 7,59 (1H, d, *J* = 9,1 Hz), 7,10 (2H, d, *J* = 8,2 Hz), 6,74 (2H, d, *J* = 8,2 Hz), 6,31 (1H, d, *J* = 9,2 Hz) 4,57 (2H, t, *J* = 6,5 Hz), 4,26 (1H, dd, *J* = 13,5, 0,2 Hz), 3,49-3,66 (2H, m), 3,34 (3H,s), 3,28 (2H, t, *J* = 6,5 Hz), 3,05-3,11 (1H, m), 2,89-2,97 (1H, m), 1,19 (3H, t, *J* = 7,0 Hz)	para BR 411 $(M+H)^+$	
D-20		^{1}H RMN (MeOH-d_4, 400 MHz): 8,31 (1H, s), 7,59 (1H, d, *J* = 9,1 Hz), 7,34 (2H, d, *J* = 8,2 Hz), 7,24 (2H, d, *J* = 8,2 Hz), 6,31 (1H, d, *J* = 9,2 Hz) 4,57 (2H, t, *J* = 6,5 Hz), 4,26 (1H, dd, *J* = 13,5, 0,2 Hz), 3,49-3,66 (2H, m), 3,28 (2H, t, *J* = 6,5 Hz), 3,05-3,11 (1H, m), 2,89-2,97 (1H, m), 1,19 (3H, t, *J* = 7,0 Hz)	para BR 400 $(M+H)^+$	
D-21		^{1}H RMN (MeOH-d_4, 400 MHz): 8,31 (1H, s), 7,59 (1H, d, *J* = 9,1 Hz), 6,94 (2H, d, *J* = 8,2 Hz), 6,66 (2H, d, *J* = 8,3 Hz), 6,31 (1H, d, *J* = 9,2 Hz) 4,57 (2H, t, *J* = 6,5 Hz), 4,26 (1H, dd, *J* = 13,5, 0,2 Hz), 4,01 (2H, c, *J* = 6,9 Hz), 3,49-3,66 (2H, m), 3,28 (2H, t, *J* = 6,5 Hz), 3,05-3,11 (1H, m), 2,89-2,97 (1H, m), 1,40 (3H, t, *J* = 7,0 Hz),	para BR 360 $(M+H)^+$	

		1,19 (3H, t, J = 7,0 Hz)		
D-22		^{1}H RMN (MeOH-d_4, 400 MHz): 8,31 (1H, s), 7,59 (1H, d, J = 9,1 Hz), 6,97 (2H, d, J = 8,2 Hz), 6,77 (2H, d, J = 8,2 Hz), 6,31 (1H, d, J = 9,2 Hz) 4,57 (2H, t, J = 6,5 Hz), 4,28 (1H, dd, J = 13,5, 0,2 Hz), 3,78 (3H, s), 3,49-3,66 (2H, m), 3,28 (2H, t, J = 6,5 Hz), 3,05-3,11 (1H, m), 2,89-2,97 (1H, m), 1,19 (3H, t, J = 7,0 Hz)	para BR 348 (M+H)$^+$	
D-23		(MeOD, 400 MHz): 8,03 (1H, d, J = 2,8 Hz), 7,84-7,82 (2H, m), 7,35-7,34 (3H, m), 7,26 (1H, dd, J = 8,6, 2,5 Hz), 7,16 (1H, d, J = 8,6 Hz), 4,20 (2H, t, J = 6,4 Hz) 4,06 (1H, dd, J = 8,6, 4,6 Hz), 3,52-3,44 (1H, m), 3,22-3,14 (1H, m), 3,03 (1H, dd, J = 13,9, 4,6 Hz), 2,88 (2H, t, J = 6,3 Hz), 2,92 (1H, d, J = 9,1 Hz), 2,26 (3H, s), 0,94 (3H, t, J = 7,0 Hz)	para BR 397 (M+H)$^+$	
D-24		($CDCl_3$, 400 MHz): 8,25 (1H, d, J = 1,5 Hz), 7,95 (2H, dd, J = 7,6, 1,8 Hz), 7,44-7,36 (3H, m), 7,28-7,22 (2H, m), 4,19 (1H, dd, J = 7,1, 4,8 Hz), 4,02 (2H, t, J = 6,1 Hz) 3,80-3,72 (1H, m), 3,47-3,39 (1H, m), 3,34 (1H, dd, J = 15,2, 7,1 Hz), 3,20 (1H, dd, J = 15,2, 4,3 Hz), 2,67 (2H, t, J = 7,2 Hz), 2,27 (3H, s), 2,19-2,12 (2H, m), 1,17 (3H, t, J = 7,0 Hz)	para BR 411 (M+H)$^+$	
D-25		($CDCl_3$, 400 MHz): 8,16 (1H, d, J = 2,3 Hz), 7,24-7,19 (2H, m), 4,27 (2H, t, J = 6,6 Hz), 4,17 (1H, dd, J = 7,6, 3,6 Hz), 3,79-3,72 (1H, m), 3,47-3,40 (1H, m), 3,32 (1H, dd, J = 15,4, 7,6 Hz) 3,18 (1H, dd, J = 15,4, 3,5 Hz), 3,09 (2H,t, J = 6,7 Hz), 2,59 (3H, s),	para BR 351 (M+H)$^+$	

		2,34 (3H, s), 1,17 (3H, t, J = 7,0 Hz)		
D-26		(MeOD, 400 MHz): 8,01 (1H, d, J = 3,0 Hz), 7,74-7,71 (2H, m), 7,34-7,27 (3H, m), 7,24 (1H, dd, J = 8,6, 2,8 Hz), 7,14 (1H, d, J = 8,6 Hz), 4,27 (2H, t, J = 6,6 Hz) 4,06 (1H, dd, J = 8,7, 4,7 Hz), 3,51-3,44 (1H, m), 3,22-3,14 (1H, m), 3,08 (2H, t, J = 6,4 Hz), 3,02 (1H, dd, J = 14,2, 4,8 Hz), 2,89 (1H, dd, J = 13,9, 8,6 Hz), 2,34 (3H, s), 0,93 (3H, t, J = 7,1 Hz)	para BR 413 $(M+H)^+$	
D-27		(MeOD, 400 MHz): 7,86-7,82 (3H, m), 7,47 (1H, dd, J = 8,6, 2.0 Hz), 7,39-7,36 (3H, m), 6,62 (1H, d, J = 8,3 Hz), 4,14 (2H, t, J = 6,2 Hz), 3,22-3,20 (3H, m), 2,85 (2H, dd, J = 22,5, 13,9 Hz) 2,60 (2H, t, J = 7,1 Hz), 2,19 (3H, s), 2,03 (2H, dd, J = 12,9, 6,1 Hz), 1,26 (3H, s)	para BR 411 $(M+H)^+$	
D-28		(MeOD, 400 MHz): 8,02 (1H, d, J = 2,5 Hz), 7,85-7,83 (2H, m), 7,39-7,33 (3H, m), 7,26 (1H, dd, J = 8,6, 2,8 Hz), 7,20 (1H, d, J = 8,6 Hz), 3,96 (2H, t, J = 6,1 Hz) 3,20 (3H, s), 3,05 (2H, dd, J = 21,0, 13,9 Hz), 2,61 (2H, t, J = 7,2), 2,20 (3H, s), 2,07-2,01 (2H, m), 1,24 (3H, s)	para BR 411 $(M+H)^+$	
D-29		(MeOD, 400 MHz): 8,02 (1H, d, J = 2,8 Hz), 7,87-7,83 (2H, m), 7,39-7,36 (3H, m), 7,27 (1H, dd, J = 8,6, 2,8 Hz), 7,19 (1H, d, J = 8,6 Hz), 4,22 (2H, t, J = 6,4 Hz) 3,19 (3H, s), 3,05 (2H, dd, J = 21,2, 13,9 Hz), 2,91 (2H, t, J = 6,4), 2,29 (3H, s), 1,23 (3H, s)	para BR 397 $(M+H)^+$	
D-30		(MeOD, 400 MHz): 7,87-7,84 (3H, m), 7,48 (1H, dd, J = 8,6, 2,3 Hz), 7,41 (2H, d, J = 8,6 Hz), 6,81 (1H, d,	para BR 431 $(M+H)^+$	

		J = 8,6 Hz) 4,42 (2H, t, J = 6,6 Hz), 3,22 (3H, s), 2,91-2,88 (3H, m), 2,83 (1H, d, J = 13,9), 2,27 (3H, s), 1,25 (3H, s)		
D-31		(MeOD, 400 MHz): 8,04 (2H, d, J = 8,1 Hz), 7,84 (1H, d, J = 2,0 Hz), 7,70 (2H, d, J = 8,3 Hz), 7,48 (1H, dd, J = 8,5, 2,4 Hz), 6,60 (1H, d, J = 8,3 Hz), 4,43 (2H, t, J = 6,6 Hz), 3,22 (3H, s), 2,91 (2H, t, J = 6,4 Hz), 2,88 (1H, d, J = 14,2 Hz) 2,82 (1H, d, J = 14,2 Hz), 2,28 (3H, s), 1,25 (3H, s)	para BR 465 $(M+H)^+$	
D-32		(MeOD, 400 MHz): 7,84 (1H, d, J = 2,0 Hz), 7,47 (1H, dd, J = 8,5, 2,4 Hz), 6,59 (1H, d, J = 8,6 Hz), 4,32 (2H, t, J = 6,6 Hz), 3,23 (3H, s), 2,89 (1H, d, J = 14,2 Hz), 2,83 (1H, d, J = 13,9 Hz), 2,78 (2H, t, J = 6,7 Hz), 2,64 (1H, tt, J = 11,6, 3,5 Hz) 2,13 (3H, s), 1,93-1,89 (2H, m), 1,75-1,71 (2H, m), 1,65-1,62 (1H, m), 1,50-1,40 (2H, m), 1,37-1,27 (2H, m), 1,26 (3H, s), 1,23-1,19 (1H, m)	para BR 403 $(M+H)^+$	
D-33		(MeOD, 400 MHz): 7,85 (1H, d, J = 2,3 Hz), 7,77 (2H, dd, J = 7,6, 1,8 Hz), 7,47 (1H, dd, J = 8,6, 2,3 Hz), 7,39-7,31 (3H, m), 6,61 (1H, d, J = 8,6 Hz), 4,49 (2H, t, J = 6,7 Hz), 3,23 (3H, s), 3,11 (2H, t, J = 6,7 Hz), 2,89 (1H, d, J = 13,9 Hz), 2,83 (1H, d, J = 14,2 Hz) 2,36 (3H, s), 1,26 (3H, s)	para BR 413 $(M+H)^+$	
D-34		(MeOD, 400 MHz): 7,84 (1H, d, J = 2,3 Hz), 7,43 (1H, dd, J = 8,5, 2,4 Hz), 7,17 (2H, dd, J = 8,1, 0,8 Hz), 7,09-7,05 (1H, m), 6,94 (1H, dt, J = 7,8, 1,0 Hz), 6,53 (1H, d, J = 8,3 Hz), 4,49 (2H, t, J = 5,3 Hz), 3,87 (2H, t, J	para BR 388 $(M+H)^+$	

		= 5,3 Hz), 3,23 (3H, s), 3,18 (3H, s), 2,88 (1H, d, *J* = 13,9 Hz) 2,82 (1H, d, *J* = 13,9 Hz), 1,26 (3H, s)		
D-35		(Dimetil sulfóxido-d_6, 300 MHz): 7,91 (3H, m), 7,49 (4H, m), 7,40 (3H, m), 6,69 (1H, d, *J* = 8,5 Hz), 4,44 (2H, t, *J* = 6,7 Hz), 3,44 (2H, m), 3,16 (3H, s), 2,89 (2H, m), 2,31 (3H, s), 1,19 (3H, s)	para BR 395 $(M)^-$	Calculado para $C_{22}H_{24}N_2O_3$ C 66,65 H 6,10 N 7,07. Encontrado: $C_{22}H_{24}N_2O_3 0,06H_2O$ C 66,16 H 6,15 N 6,96
D-36		(MeOD, 400 MHz): 7,83 (1H, d, *J* = 1,8 Hz), 7,69 (1H, s), 7,65 (1H, d, *J* = 7,6 Hz), 7,48 (1H, dd, *J* = 8,6, 2,3 Hz), 7,25 (1H, t, *J* = 7,6 Hz), 7,19 (1H, d, *J* = 7,6 Hz), 6,59 (1H, d, *J* = 8,3 Hz), 4,39 (2H, t, *J* = 6,6 Hz), 3,19 (3H, s), 2,87 (2H, t, *J* = 6,4 Hz) 2,87 (1H, d, *J* = 13,9 Hz), 2,80 (1H, d, *J* = 13,9 Hz), 2,30 (3H, s), 2,24 (3H, s), 1,21 (3H, s)	para BR 411 $(M+H)^+$	
D-37		(MeOD, 400 MHz): 7,83 (1H, d, *J* = 2,3 Hz), 7,79-7,76 (2H, m), 7,48 (1H, dd, *J* = 8,5, 2,4 Hz), 6,90 (2H, d, *J* = 8,8 Hz), 6,59 (1H, d, *J* = 8,6 Hz), 4,38 (2H, t, *J* = 6,7 Hz), 4,00 (2H, c, *J* = 7,1 Hz), 3,21 (3H, s), 2,88 (1H, d, *J* = 13,9 Hz), 2,86 (2H, t, *J* = 6,6 Hz) 2,81 (1H, d, *J* = 13,9 Hz), 2,22 (3H, s), 1,31 (3H, t, *J* = 7,0 Hz), 1,24 (3H, s)	para BR 441 $(M+H)^+$	
D-38		($CDCl_3$, 400 MHz): 7,93 (1H, d, *J* = 2,3 Hz), 7,45 (1H, dd, *J* = 8,5, 2,4 Hz), 6,63 (1H, d, *J* = 8,6 Hz), 4,40 (2H, t, *J* = 6,6 Hz), 3,37 (3H, s), 3,05-2,96 (1H, m), 2,97 (1H, d, *J* = 14,4 Hz), 2,92 (1H, d, *J* = 14,4 Hz), 2,86 (2H, t, *J* = 6,7 Hz), 2,20 (3H, s), 1,43	para BR 383 $(M+H)^+$	

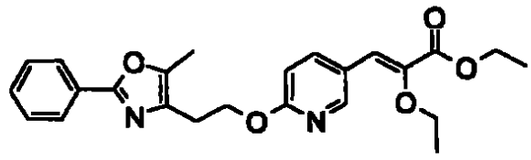
		(3H, s), 1,30 (3H, s), 1,28 (3H, s)		
D-39		(MeOD, 400 MHz): 7,82 (1H, d, *J* = 2,0 Hz), 7,44 (1H, dd, *J* = 8,6, 2,3 Hz), 6,57 (1H, d, *J* = 8,6 Hz), 6,45 (1H, s), 4,39 (2H, t, *J* = 6,4 Hz), 4,00 (3H, s), 3,20 (3H, s), 2,86 (2H, t, *J* = 6,6 Hz), 2,68 (1H, d, *J* = 14,2 Hz), 2,80 (1H, d, *J* = 14,2 Hz), 2,22 (3H, s), 2,14 (3H, s), 1,23 (3H, s)	para BR 415 $(M+H)^+$	
D-40		(MeOD, 400 MHz): 7,82 (1H, d, *J* = 2,3 Hz), 7,44 (1H, dd, *J* = 8,0, 1,9 Hz), 7,34-7,29 (2H, m), 7,22 (2H, d, *J* = 8,6 Hz), 7,09-7,03 (1H, m), 6,98-6,91 (4H, m), 6,80 (1H, d, *J* = 8,6 Hz), 4,33 (2H, t, *J* = 7,1 Hz), 3,20 (3H, s), 3,00 (2H, t, *J* = 7,0 Hz), 2,82 (1H, d, *J* = 14,2 Hz), 2,80 (1H, d, *J* = 14,2 Hz) 1,23 (3H, s)	para BR 408 $(M+H)^+$	
D-41		(MeOD, 400 MHz): 7,81 (1H, d, *J* = 2,3 Hz), 7,44 (1H, dd, *J* = 8,6, 2,3 Hz), 7,27 (2H, d, *J* = 8,6 Hz), 7,07 (2H, d, *J* = 7,8 Hz), 6,57 (1H, d, *J* = 8,6 Hz), 4,33 (2H, t, *J* = 6,7 Hz), 3,20 (3H, s), 2,97 (2H, t, *J* = 6,7 Hz), 2,84 (1H, d, *J* = 14,2 Hz) 2,82 (1H, d, *J* = 14,2 Hz), 1,24 (3H, s)	para BR 400 $(M+H)^+$	
D-42		(MeOD, 400 MHz): 7,83 (1H, d, *J* = 1,8 Hz), 7,65 (1H, d, *J* = 7,6 Hz), 7,46 (1H, dd, *J* = 8,6, 2,3 Hz), 7,29 (1H, s), 7,25 (1H, t, *J* = 7,6 Hz), 7,19 (1H, d, *J* = 7,6 Hz), 6,59 (1H, d, *J* = 8,3 Hz), 4,39 (2H, t, *J* = 6,6 Hz), 3,19 (3H, s), 2,87 (2H, t, *J* = 6,4 Hz) 2,67 (1H, d, *J* = 13,9 Hz), 2,60 (1H, d, *J* = 13,9 Hz), 2,24 (3H, s), 1,21 (3H, s)	para BR 415 $(M+H)^+$	
D-43		(MeOD, 400 MHz): 7,81 (1H, d, *J* = 2,3 Hz), 7,45-7,38 (2H, m), 7,32-7,24	para BR 427 $(M+H)^+$	

		(2H, m), 6,81 (1H, dd, J = 8,0, 2,4 Hz), 6,58 (1H, d, J = 8,3 Hz), 4,38 (2H, t, J = 6,7 Hz), 3,74 (3H, s), 3,18 (3H, s), 2,88 (2H, t, J = 6,7 Hz), 2,85 (1H, d, J = 13,9 Hz), 2,79 (1H, d, J = 13,9 Hz), 2,22 (3H, s), 1,22 (3H, s)		

Preparaciones de materiales de partida para los Ejemplos D-1 a D-43 (Preparaciones d-1 a d-42):

Preparación d-1

2-Etoxi-3-{6-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridin-3-il}acrilato de etilo



Se añadió gota a gota *N,N,N',N'*-tetrametilguanidina (0,305 ml, 2,43 mmol) a una solución de 6-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]nicotinaldehído (250 mg, 0,811 mmol) y cloruro de (1,2-dietoxi-2-oxoetil)(trifenil)fosfonio (696 mg, 1,62 mmol) en cloroformo (4 ml). La mezcla se agitó durante 16 horas y después se repartió entre una solución saturada de cloruro amónico y acetato de etilo. La fase orgánica se lavó con salmuera, se secó sobre sulfato de magnesio, se filtró y se evaporó. El residuo se purificó por cromatografía en columna ultrarrápida (1:2 de acetato de etilo:hexanos) para producir el compuesto del título en forma de un sólido blanco (330 g, 96%).

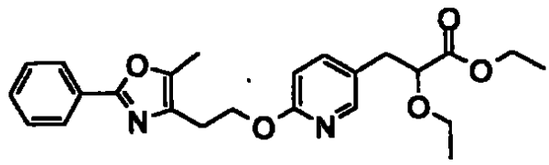
EMBR: (*m/z*): 423 $(M+H)^+$.

^{1}H RMN ($CDCl_3$, 300 MHz) 8,42 (1H, m), 8,10 (1H, m), 7,97 (1H, m), 7,40 (2H, m), 7,28 (3H, m), 6,90 (1H, s), 6,73 (1H, m), 4,60 (2H, t, J = 7 Hz), 4,30 (2H, c,

J = 7 Hz), 4,01 (2H, c, *J* = 7 Hz), 2,99 (2H, t, *J* = 7 Hz), 2,34 (3H, s), 1,36 (6H, m).

Preparación d-2

2-Etoxi-3-{6-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridin-3-il}propanoato de etilo

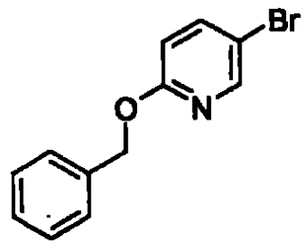


Una solución de 2-etoxi-3-{6-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridin-3-il}acrilato de etilo (328 mg, 0,776 mmol) en etanol (10 ml) se hidrogenó a 344,73 kPa sobre paladio al 10% sobre carbono (33 mg) durante 3 horas. La mezcla se filtró a través de celite y los sólidos se lavaron con acetato de etilo. El filtrado y los lavados se evaporaron y el residuo se purificó por cromatografía en columna ultrarrápida (1:2 de acetato de etilo:hexano) para producir el compuesto del título en forma de un aceite incoloro (183 mg, 56%). EMBR (*m/z*): 425 $(M+H)^+$.

^{1}H RMN ($CDCl_3$, 300 MHz) 7,99 (3H, m), 7,42 (4H, m), 6,65 (1H, m), 4,54 (2H, t, J = 7 Hz), 4,18 (2H, c, *J* = 7 Hz), 3,93 (1H, m), 3,63 (1H, m), 3,36 (1H, m), 2,.90 (4H, m), 2,33 (3H, s), 1,25 (3H, t, *J* = 7 Hz), 1,16 (3H, t, *J* = 7 Hz).

Preparación d-3

Preparación de 2-(benciloxi)-5-bromopiridina



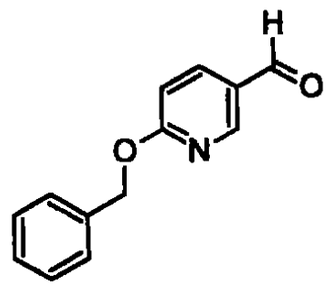
A una solución de 5-bromopiridin-2(1H)-ona (100 mmol, 17,4 g, 1,0 equiv.) en benceno (170 ml) se le añadió carbonato de plata (I) (67,0 mmol, 18,5 g, 0,67 equiv.). El matraz se cubrió con una lámina de aluminio y después se añadió bromuro de bencilo (120 mmol, 20,5 g, 1,2 equiv.) mediante una jeringa en una corriente estacionaria. La mezcla se calentó a 50°C y se agitó en un matraz durante aproximadamente 24 horas. El EM/CL de la mezcla de reacción indica dos picos tanto con M+H = 265 que corresponde al peso molecular deseado. Basándose en las polaridades relativas, se pensó que el pico más polar era el producto N-alquilado y constaba de aproximadamente un 20% del total. La mezcla de reacción se dejó enfriar a temperatura ambiente y la sal de plata se retiró por filtración de la mezcla a través de una capa de celite. La torta de filtro se lavó con benceno y la capa orgánica se lavó dos veces con bicarbonato sódico al 2% y dos veces con agua. La capa orgánica se secó sobre sulfato de magnesio y se concentró al vacío. El residuo bruto se purificó sobre un Biotage Sp4 65i sobre un gradiente de hexanos al 5-95% en acetato de etilo para producir el compuesto del título en forma de un aceite dorado (25,1 g, 95%).

EMBR: 265 $(M+H)^+$.

^{1}H RMN (DMSO-d_6, 400 MHz): 8,29 (1H, s), 7,72 (1H, d, J = 8,5 Hz), 7,31-7,43 (5H, m), 6,54 (1H, d, J = 8,5 Hz), 5,34 (2H, s).

Preparación d-4

Preparación de 6-(benciloxi)nicotinaldehído



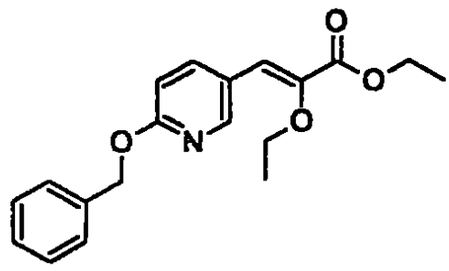
Se añadió gota a gota n-butil litio (2,5 M, 95,9 mmol, 38,4 ml, 1,05 eq.) mediante una jeringa a una solución agitada de 2-(benciloxi)-5-bromopiridina (91,3 mmol, 24,1 g, 1,0 equiv.) en THF (260 ml, c = 0,35) enfriada a -78°C. Después de completarse la adición, la solución se dejó en agitación a la misma baja temperatura durante 1 hora. En este punto, se añadió gota a gota *N,N*-dimetilformamida (183 mmol, 13,4 g, 2,0 equiv.) como una solución en 5 ml de THF. Se continuó agitando a la misma baja temperatura durante 30 minutos más, momento en el que la reacción se interrumpió por la adición de bicarbonato sódico al 5%. La mezcla se transfirió a un embudo de decantación y se extrajo con éter (3 x 250 ml). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato de magnesio anhidro y se concentraron al vacío. El aceite amarillo resultante se purificó sobre un Biotage Sp4 65i sobre un gradiente de hexanos al 0-50% en acetato de etilo para producir el compuesto del título (14,1 g, 73%).

EMBR: 214 $(M+H)^+$.

^{1}H RMN (DMSO-d_6, 400 MHz): 10,02 (1H, s), 8,86 (1H, s), 8,03 (1H, d, *J* = 9,3 Hz), 7,31-7,43 (5H, m), 6,50 (1H, d, *J* = 9,3 Hz), 5,33 (2H, s).

Preparación d-5

Preparación de (2Z)-3-[6-(benciloxi)piridin-3-il]-2-etoxiacrilato de etilo



A una solución de 6-(benciloxi)nicotinaldehído (1,0 equiv., 33,1 mmol, 7,05 g) y cloruro de (1,2-dietoxi-2-oxoetil)(trifenil)fosfonio (2,0 equiv., 66,2 mmol, 28,4 g) en cloroformo (165 ml, 0,2 M) se le añadió tetrametilguanidina (3,0 equiv., 99,3 mmol, 11,4 g). El matraz se tapó con un tapón de vidrio hueco y se agitó a temperatura ambiente durante una noche. El análisis por TLC después de aproximadamente 18 horas indicó la presencia de una pequeña cantidad de material de partida sin reaccionar. La mezcla de reacción se calentó a reflujo y se reanalizó por TLC cada 2 horas. La reacción se interrumpió con cloruro amónico saturado. Las capas se separaron y la capa orgánica se lavó con salmuera, se secó sobre sulfato de magnesio y se concentró al vacío. Precipitó una gran cantidad de óxido de trifenilfosfina. El residuo se trituró con éter y se filtró. La torta de filtró se lavó con éter y se concentró con los filtrados combinados al vacío para producir un sólido amarillo pálido que se disolvió en una cantidad mínima de DCM y se cargó en un Biotage Sp4 65i y se eluyó sobre un gradiente de hexanos 10-100% en acetato de etilo. Se obtuvieron 12,3 g de un aceite transparente incoloro (37,6 mmol, cuant.).

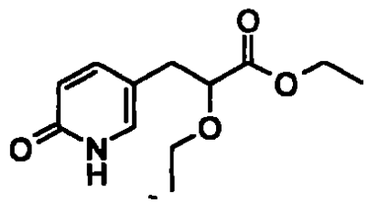
EMBR: 328 $(M+H)^+$.

^{1}H RMN (DMSO-d_6, 400 MHz): 8,33 (1H, s), 7,92 (1H, d, J = 8,0 Hz), 7,31-7,43 (5H, m), 6,76 (1H, d, J = 8,1 Hz), 6,60 (1H, s), 5,37 (2H, s), 4,23 (2H, c, J = 7,1

Hz), 3,90-3,99 (2H, m), 1,34 (6H, dt, *J* = 15,8, 7,0 Hz).

Preparación d-6

Preparación de 2-etoxi-3-(6-oxo-1,6-dihidropiridin-3-il)propanoato de etilo



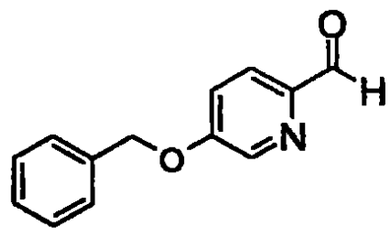
A un recipiente agitador Parr que contenía una solución de (2Z)-3-[6-(benciloxi)piridin-3-il]-2-etoxiacrilato de etilo en etanol se le añadió Pd al 10% sobre carbono (~ 1,23 g). El recipiente se purgó con hidrógeno y se desgasificó a presión reducida tres veces. La mezcla se puso a 344,73 kPa de hidrógeno y se agitó a temperatura ambiente durante una noche. Después de ~20 horas, la agitación se detuvo y el recipiente se desgasificó al vacío. El análisis por TLC indicó el consumo del material de partida. La mezcla se filtró a través de una capa de celite para retirar el paladio. La torta de filtro se lavó con una porción adicional de etanol. Esta solución se concentró al vacío para producir la piridona reducida y desbencilada en forma de un aceite dorado. Este aceite se purificó sobre un Biotage Sp4, 65i, 80 ml/min sobre un gradiente de MeOH al 0-10% en DCM para producir 2,77 g de un aceite incoloro transparente (11,6 mmol, 31%).

EMBR: 240 $(M+H)^+$.

^{1}H RMN (DMSO-d_6, 400 MHz): 7,29 (1H, d, *J* = 9,5 Hz), 7,19 (1H, d, *J* = 5,2 Hz), 6,55 (1H, d, *J* = 9,5 Hz), 4,20 (2H, c, *J* = 7,0 Hz), 4,10 (1H, dd, *J* = 9,6, 0,3 Hz), 3,59-3,73 (2H, m), 2,65-2,70 (1H, m), 2,53-2,61 (1H, m), 1,23 (6H, td, *J* = 7,0, 3,6 Hz).

Preparación d-7

5-Benciloxi-piridina-2-carbaldehído



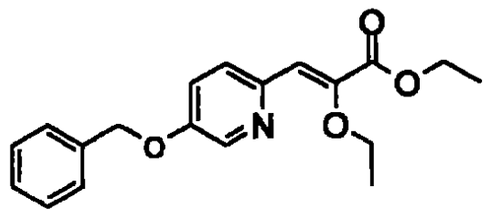
A una solución de (5-benciloxi-piridin-2-il)-metanol (2,3619 g, 10,9728 mmol) en diclorometano (120 ml) y piridina (2,68 ml, 32,9184 mmol) se le añadió 1,1,1-triacetoxi-1,1-dihidro-1,2-bencidioxol-3-(1*H*)-ona (6,9812 g, 16,4592 mmol). La solución resultante se agitó en una atmósfera de nitrógeno a temperatura ambiente durante 16 horas y después se diluyó con éter dietílico (100 ml) seguido de la concentración parcial a presión reducida. El residuo se recogió en éter dietílico (150 ml) y los precipitados se retiraron por extracción con 1:1 de tiosulfato sódico acuoso al 10%:bicarbonato sódico acuoso saturado (2 x 100 ml). La capa orgánica se lavó con agua (100 ml) y cloruro sódico acuoso saturado (100 ml), se secó (sulfato de magnesio anhidro), se filtró y concentró al vacío produciendo el compuesto del título puro (1,1694 g, 50%) en forma de un aceite amarillo pálido.

EMBR (*m/z*): 214 $(M+H)^+$.

^{1}H RMN ($CDCl_3$, 300 MHz): 9,98 (1H, d, *J* = 0,8 Hz), 8,49 (1H, d, *J* = 2,5 Hz), 7,94 (1H, d, *J* = 8,7 Hz), 7,44-7,40 (4H, m), 7,38-7,33 (2H, m), 5,19 (2H, s).

Preparación d-8

Éster etílico del ácido 3-(5-benciloxi-piridin-2-il)-2-etoxi-acrílico



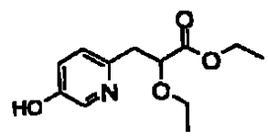
A una solución de 5-benciloxi-piridina-2-carbaldehído (1,1694 g, 5,4842 mmol), cloruro de (etoxicarbonil-metoxi-metil)-trifenil-fosfonio (4,7043 g, 10,9684 mmol) en cloroformo (30 ml), en una atmósfera de nitrógeno a temperatura ambiente, se le añadió gota a gota tetrametilguanidina (2,1 ml, 16,4526 mmol). La solución resultante se agitó durante 16 horas y después se inactivó con cloruro amónico acuoso saturado (50 ml). Las fases se separaron y la fase orgánica se lavó con cloruro sódico acuoso saturado (50 ml), se secó (sulfato de magnesio anhidro), se filtró y se concentró al vacío para proporcionar el producto bruto. El residuo se purificó por cromatografía en columna ultrarrápida (hexanos a acetato de etilo) para producir el compuesto del título puro (1,8051 g, 100%) en forma de un aceite amarillo.

EMBR (*m/z*): 328 $(M+H)^+$

^1H RMN ($CDCl_3$, 300 MHz):8,37 (1H, d, *J* =2,6 Hz), 8,18 (1H, d, *J* = 8,9 Hz), 7,44-7,33 (5H, m), 7,25 (1H, dd, *J* = 8,9,3,0 Hz), 7,13 (1H, s), 5,13 (2H, s), 4,27 (2H, c, *J* = 7,2 Hz), 4,05 (2H, c, *J* = 7,2 Hz), 1,35 (3H, t, *J* =7,0 Hz), 1,34 (3H, t, *J* = 7,0 Hz).

Preparación d-9

Éster etílico del ácido 2-etoxi-3-(5-hidroxi-piridin-2-il)propiónico



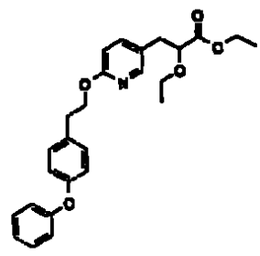
A una solución del éster etílico del ácido 3-(5-benciloxi-piridin-2-il)-2-etoxi-acrílico (1,8051 g, 5,5144 mmol) en etanol seco (40 ml) se le añadió paladio (0,1805 g, 10% en peso sobre carbono activado). La solución resultante se agitó a temperatura ambiente en una atmósfera de hidrógeno (344,73 kPa) durante 16 horas. La solución resultante se filtró a través de una capa de Celite de 7,62 cm y se lavó con etanol (200 ml). Después, el filtrado se concentró al vacío para producir el compuesto del título puro (1,2231 g, 93%) en forma de un aceite amarillo pálido.

EMBR (*m/z*): 240 $(M+H)^+$.

^{1}H RMN ($CDCl_3$, 300 MHz): 8,14 (1H, s), 7,20-7,11 (2H, m), 4,19-4,10 (3H, m), 3,71 (1H, c, *J* = 7,0 Hz), 3,63-3,53 (1H, m),3,36-3,26 (1H, m), 3,18-3,03 (1H, m), 1,18 (3H, t, *J* = 7,2 Hz), 1,07 (3H, t, *J* = 7,1 Hz).

Preparación d-10

2-Etoxi-3-[6-[2-(4-fenoxifenil)etoxi]piridin-3-il]propanoato de etilo

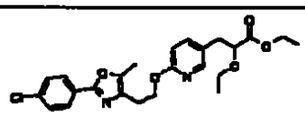
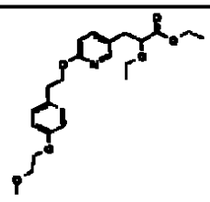
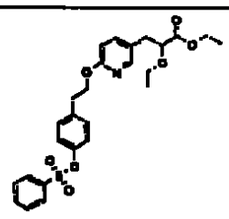


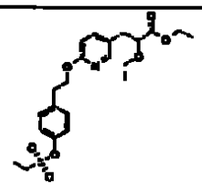
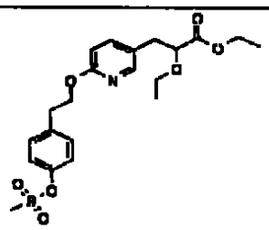
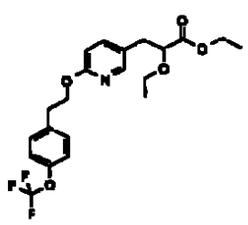
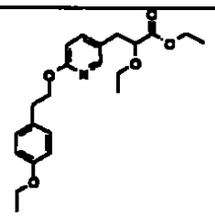
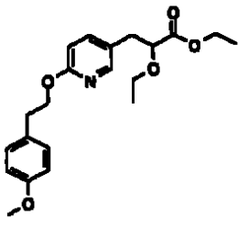
A una solución purgada con argón de la bromopiridina apropiada (0,636 mmol) en tolueno (12 ml) se le añadió acetato de paladio (II) (11,4 mg, 0,0508

mmol) y 2-(di-t-butilfosfino)-1,1'-binaftilo racémico (25,4 mg, 0,0636 mmol). Se dejó que se formara el complejo activado durante aproximadamente diez minutos, punto en el que se añadieron carbonato de cesio (414 mg, 1,27 mmol) y el alcohol apropriado (0,956 mmol). La mezcla se calentó a 115ºC y se agitó a esta temperatura durante aproximadamente 12-18 horas. La mezcla se enfrió a temperatura ambiente y se filtró a través de una capa de sílice. La capa de filtro se lavó con 2-3 alícuotas de acetato de etilo y los filtrados orgánicos combinados se combinaron y se concentraron al vacío. El residuo resultante se purificó otra vez por cromatografía ultrarrápida o se sometió al procedimiento de hidrólisis general.

Preparaciones d-11 a d-18

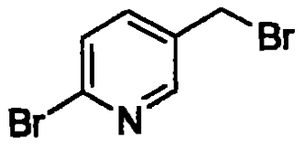
Las preparaciones d-11 a d-18 se prepararon por procedimientos análogos a los usados para la Preparación d-10

Prep. Nº	Estructura	^{1}H, RMN	EM (*m/z*) (BR o AR)
d-11			
d-12			
d-13			

d-14			
d-15			
d-16			
d-17			
d-18			

Preparación d-19

2-bromo-5-(bromometil)piridina



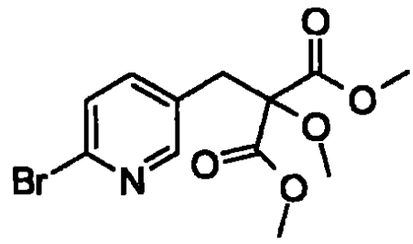
Se añadió cuidadosamente tribromuro de fósforo (100 mmol,27,1 g, 2,0 equiv.) a 2-cloro-5-hidroximetil piridina (50,0 mmol, 7,18 g, 1,0 equiv.). La piridina se agrupó y la mezcla se calentó a 160ºC. Dentro de un periodo de 5 minutos de agitación a >150ºC, la mezcla se volvió de color muy oscuro con desprendimiento de gas. La mezcla se agitó a esta misma temperatura durante aproximadamente 2,5 horas, momento en el que se enfrió a temperatura ambiente. La mezcla se enfrió adicionalmente a 0ºC, después de lo cual se añadió bicarbonato sódico saturado muy cuidadosamente (muy exotérmico). Según comenzó a ser menos vigorosa la espumación, se añadió hielo a la mezcla hasta que ceso la espumación. Después se añadió cuidadosamente bicarbonato sódico sólido hasta conseguir un pH de ~8-9. La mezcla se extrajo con acetato de etilo y la capa orgánica se lavó con salmuera y se secó sobre sulfato de magnesio anhidro. Se concentró al vacío para producir un sólido oscuro. Este material se disolvió en una cantidad mínima de DCM y se purificó usando un Biotage Sp4 65i sobre un gradiente de acetato de etilo al 0-100% en hexanos para producir el compuesto del título en forma de un sólido amarillo pálido (5,57 g, 44%).

EMBR: 252 $(M+H)^+$.

^{1}H RMN (DMSO-d_6, 400 MHz): 8,39 (1H, s), 7,59 (1H, d, J = 8,5 Hz), 7,48 (1H, d, J = 8,5 Hz), 4,46 (2H, s).

Preparación d-20

Preparación de [(6-bromopiridin-3-il)metil](metoxi)malonato de dimetilo



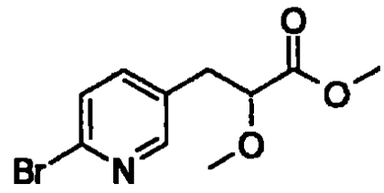
A una suspensión de *t*-butóxido potásico (46,6 mmol, 5,22 g, 1,3equiv.) en DMF anhidra (250 ml) enfriada a 0ºC se le añadió metoxi dimetilmalonato (46,6 mmol, 7,55 g, 1,3 equiv.) mediante una jeringa en pequeñas porciones. El enolato se dejó calentar durante aproximadamente 30 minutos, punto en el que se añadió por porciones 2-bromo-5-(bromometil)piridina. La mezcla de reacción se dejó calentar lentamente a temperatura ambiente durante 3 horas. La mezcla de reacción se diluyó con éter etílico y se transfirió a un embudo de decantación que contenía cloruro amónico saturado. Las capas se agitaron y se separaron y la capa orgánica se lavó con agua. La capa orgánica después se secó sobre sulfato de magnesio anhidro y se concentró al vacío. El aceite amarillo obtenido se purificó sobre un Biotage Sp4 65i sobre un gradiente de acetato de etilo al 0-100% en hexanos para producir un aceite incoloro que solidificó tras reposo (12,1 g, cuant.).

EMBR: 333 $(M+H)^+$.

^1H RMN (DMSO-d_6, 400 MHz): 8,27 (1H, s), 7,45-7,55 (2H, m), 3,82 (6H, s), 3,57 (3H, s), 3,42 (2H, s).

Preparación d-21

Preparación de 3-(6-bromopiridin-3-il)-2-metoxipropanoato de metilo



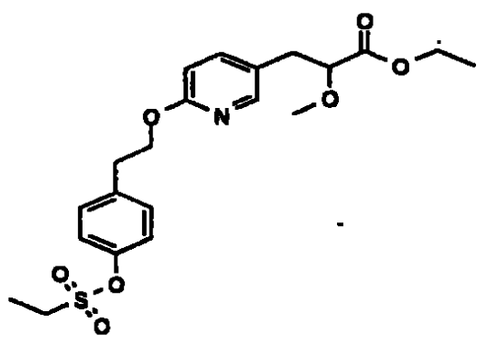
A una solución de [(6-bromopiridin-3-il)metil](metoxi)malonato de dimetilo (3,55 mmol, 1,18 g, 1,0 equiv.) en DMF anhidra (2 ml) se le añadió bromuro de litio (3,20 mmol, 0,278 g, 0,9 equiv.) seguido de agua (3,55 mmol, 0,064 g, 1,0 equiv.). La solución se puso en un baño de aceite precalentado a 165°C. Comenzó el desprendimiento de gas. La formación de burbujas cesó en 30 minutos y el EM/CL de la mezcla de reacción en este punto indicó que la reacción se había completado. Se enfrió a temperatura ambiente y se diluyó con agua. La capa acuosa se extrajo con éter dietílico (4 x 25 ml). Las capas orgánicas combinadas se lavaron con salmuera. La capa orgánica se secó sobre sulfato de magnesio anhidro y se concentró al vacío para producir 536 mg de un aceite pardo que fue una sola mancha por TLC. Se usó en la siguiente etapa sin purificación adicional.

EMBR: 275 $(M+H)^+$.

^{1}H RMN (DMSO-d_6, 400 MHz): 8,23 (1H, s), 7,42-7,51 (2H, m), 4,26 (1H,d, J = 8,1 Hz), 3,79 (3H, s), 3,51 (3H, s), 2,97-3,03 (1H, m), 2,82-2,88 (1H, m).

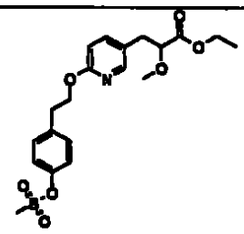
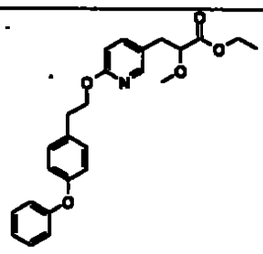
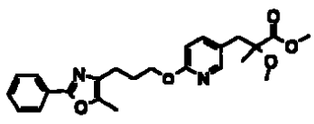
Preparación d-22

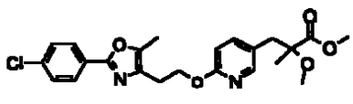
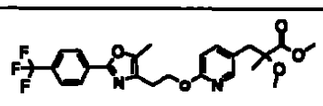
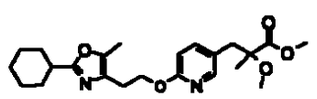
3-[6-(2-{4-[(Etilsulfonil)oxi]fenil}etoxi)piridin-3-il]-2-metoxipropanoato de etilo

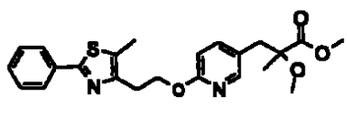
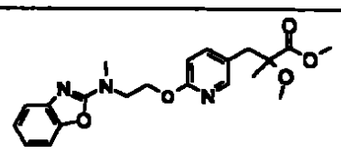
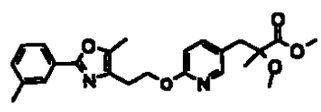


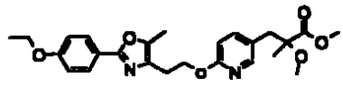
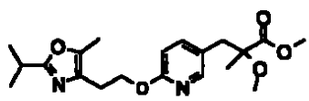
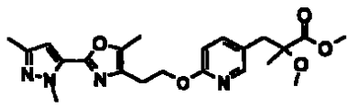
Preparaciones d-23 a d-38

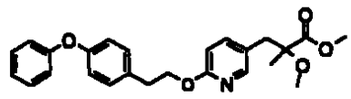
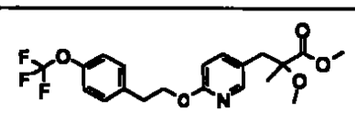
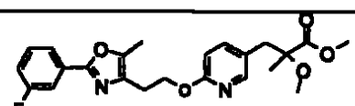
Las Preparaciones d-23 a d-38 se prepararon por procedimientos análogos a los usados para la Preparación d-22

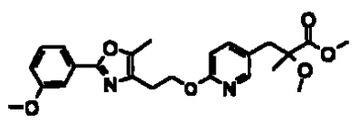
Prep. Nº	Estructura	^{1}H, RMN	EM (*m/z*) (BR o AR)
d-23			
d-24			
d-25		($CDCl_3$, 300 MHz) 7,90-7,99 (3H, m), 7,35-7,47 (4H, m), 6,65 (1H, d, *J* = 8,5 Hz), 4,27 (2H, t, *J* = 6,3 Hz), 4,17 (2H, t, *J* = 7,0 Hz), 3,29 (3H, s), 2,91 (2H, c, *J* = 14,1 Hz), 2,66 (2H, t, *J* 7,4 Hz), 2,27 (3H, s),	para BR 439 $(M+H)^+$

		2,16 (3H, s), 2,13 (2H, m), 1,25 (3H, t, *J* = 7,2 Hz)	
d-26		($CDCl_3$, 400 MHz) 7,91-7,88 (3H, m), 7,41 (1H, dd, *J* = 8,6, 2,5 Hz), 7,39-7,36 (2H, m), 6,62 (1H, d, *J* = 8,3 Hz), 4,51 (2H, t, *J* = 6,8 Hz), 3,70 (3H, s), 3,28 (3H, s), 2,97-2,93 (3H, m), 2,86 (1H, c, *J* = 14,2 Hz), 2,32 (3H, s), 1,32 (3H, s)	para BR 445 $(M+H)^+$
d-27		($CDCl_3$, 400 MHz) 8,07 (2H, d, *J* = 8,07 Hz), 7,91 (1H, d, *J* = 2,3 Hz), 7,66 (2H, d, *J* = 8,3 Hz), 7,41 (1H, dd, *J* = 8,5, 2,4 Hz), 6,62 (1H, d, *J* = 8,3 Hz), 4,52 (2H, t, *J* = 6,7 Hz), 3,70 (3H, s), 3,28 (3H, s), 2,97 (2H, t, *J* = 6,7 Hz), 2,95 (1H, d, *J* = 14,2 Hz), 2,86 (1H, d, *J* = 14,2 Hz), 2,34 (3H, s), 1,33 (3H, s)	para BR 479 $(M+H)^+$
d-28		($CDCl_3$, 400 MHz) 7,90 (1H, d, *J* = 2,3 Hz), 7,41 (1H, dd, *J* = 8,5, 2,4 Hz), 6,61 (1H, d, *J* = 8,3 Hz), 4,42 (2H, t, *J* = 6,8 Hz), 3,71 (3H, s), 3,29 (3H, s), 2,95 (1H, d, *J* = 13,9 Hz), 2,86 (1H, d, *J* = 14,2 Hz), 2,86 (2H, t, *J* = 7,1 Hz), 2,67 (1H, tt, *J* = 11,6, 3,5 Hz), 2,19 (3H, s), 2,02-1,98 (2H, m), 1,81-1,77 (2H, m), 1,69-1,65 (1H, m), 1,54-1,46 (2H, m), 1,38-1,31 (2H, m), 1,33 (3H, s), 1,28-1,24 (1H, m)	para BR 417 $(M+H)^+$

d-29		($CDCl_3$, 400 MHz) 7,82 (1H, d, *J* = 2,3 Hz), 7,85 (2H, dd, *J* = 8,0, 1,6 Hz), 7,41 (1H, dd, *J* = 8,5, 2,4 Hz), 7,39-7,35 (3H, m), 6,63 (1H, d, *J* = 8,6 Hz), 4,59 (2H, t, *J* = 7,0 Hz), 3,70 (3H, s), 3,28 (3H, s), 3,18 (2H, t, *J* = 7,0 Hz), 2,95 (1H, d, *J* = 14,2 Hz), 2,87 (1H, d, *J* = 14,2 Hz), 2,42 (3H, s), 1,33 (3H, s)	para BR 427 $(M+H)^+$
d-30		($CDCl_3$, 400 MHz) 7,90 (1H, d, *J* = 2,3 Hz), 7,41 (1H, dd, *J* = 8,5, 2,4 Hz), 7,33 (1H, d, *J* = 7,6 Hz), 7,21 (1H, d, *J* = 7,6 Hz), 7,13 (1H, dt, *J* = 7,6, 1,0 Hz), 6,97 (1H, dt, *J* = 7,8, 1,3 Hz), 6,60 (1H, d, *J* = 8,6 Hz), 4,56 (2H, t, *J* = 5,4 Hz), 3,92 (2H, t, *J* = 5,4 Hz), 3,70 (3H, s), 3,28 (6H, s), 2,95 (1H, d, *J* = 13,9 Hz), 2,86 (1H, d, *J* = 14,2 Hz), 1,32 (3H, s)	para BR 400 $(M+H)^+$
d-31		($CDCl_3$, 400 MHz) 7,91 (1H, d, *J* = 2,3 Hz), 7,81 (1H, s), 7,75 (1H, d, *J* = 7,8 Hz), 7,41 (1H, dd, *J* = 8,5, 2,4 Hz), 7,29 (1H, t, *J* = 7,7 Hz), 7,19 (1H, d, *J* = 7,6 Hz), 6,62 (1H, d, *J* = 8,3 Hz), 4,52 (2H, t, *J* = 6,8 Hz), 3,70 (3H, s), 3,28 (3H, s), 2,96 (2H, t, *J* = 6,8 Hz), 2,95 (1H, d, *J* = 13,9 Hz), 2,86 (1H, d, *J* = 13,9 Hz), 2,38 (3H, s), 2,32 (3H,	para BR 425 $(M+H)^+$

		s), 1,33 (3H, s)	
d-32		($CDCl_3$, 400 MHz) 7,91 (1H, d, *J* = 2,0 Hz), 7,89-7,86 (2H, m), 7,59 (1H, dd, *J* = 8,5, 2,2 Hz), 6,92-6,90 (2H, m), 6,62 (1H, d, *J* = 8,3 Hz), 4,51 (2H, t, *J* = 6,8 Hz), 4,06 (2H, c, *J* = 7,1 Hz), 3,70 (3H, s), 3,28 (3H, s), 2,95 (2H, t, *J* = 6,8 Hz), 2,96 (1H, d, *J* = 13,9 Hz), 2,87 (1H, d, *J* = 13,9 Hz), 2,30 (3H, s), 1,42 (3H, t, *J* = 7,1 Hz), 1,33 (3H, s)	para BR 455 $(M+H)^+$
d-33		($CDCl_3$, 400 MHz) 7,90 (1H, d, *J* = 2,3 Hz), 7,41 (1H, dd, *J* = 8,5, 2,4 Hz), 6,61 (1H, d, *J* = 8,3 Hz), 4,42 (2H, t, *J* = 6,8 Hz), 3,70 (3H, s), 3,28 (3H, s), 3,00-2,93 (1H, m), 2,95 (1H, d, *J* = 14,2 Hz), 2,86 (2H, t, *J* = 6,8 Hz), 2,86 (1H, d, *J* = 14,2 Hz), 2,20 (3H, s), 1,33 (3H, s), 1,30 (3H, s), 1,28 (3H, s)	para BR 377 $(M+H)^+$
d-34		($CDCl_3$, 400 MHz) 7,91 (1H, d, *J* = 2,3 Hz), 7,42 (1H, dd, *J* = 8,5, 2,4 Hz), 6,61 (1H, d, *J* = 8,3 Hz), 6,48 (1H, s), 4,51 (2H, t, *J* = 6,7 Hz), 4,15 (3H, s), 3,71 (3H, s), 3,28 (3H, s), 2,96 (1H, d, *J* = 13,9 Hz), 2,94 (2H, t, *J* = 6,6 Hz), 2,87 (1H, d, *J* = 13,9 Hz), 2,30 (3H, s), 2,27 (3H, s), 1,33 (3H, s)	para BR 429 $(M+H)^+$

d-35		($CDCl_3$, 400 MHz) 7,91 (1H, d, *J* = 2,3 Hz), 7,42 (1H, dd, *J* = 8,0, 1,9 Hz), 7,33-7,28 (2H, m), 7,23 (2H, d, *J* = 8,6 Hz), 7,08-7,04 (1H, m), 6,99-6,92 (4H, m), 6,64 (1H, d, *J* = 8,6 Hz), 4,45 (2H, dt, *J* = 7,1 Hz), 3,70 (3H, s), 3,20 (3H, s), 3,04 (2H, t, *J* = 7,0 Hz), 2,92 (1H, d, *J* = 14,2 Hz), 2,87 (1H, d, *J* = 14,2 Hz), 1,33 (3H, s)	para BR 422 $(M+H)^+$
d-36		($CDCl_3$, 400 MHz) 7,90 (1H, d, *J* = 2,3 Hz), 7,42 (1H, dd, *J* = 8,5, 2,4 Hz), 7,28 (2H, d, *J* = 8,6 Hz), 7,13 (2H, d, *J* = 8,1 Hz), 6,63 (1H, d, *J* = 8,3 Hz), 4,46 (2H, t, *J* = 6,8 Hz), 3,71 (3H, s), 3,28 (3H, s), 3,06 (2H, t, *J* = 6,8 Hz), 2,95 (1H, d, *J* = 14,2 Hz), 2,86 (1H, d, *J* = 13,9 Hz), 1,33 (3H, s)	para BR 414 $(M+H)^+$
d-37		($CDCl_3$, 400 MHz) 7,91 (1H, d, *J* = 2,0 Hz), 7,74 (1H, d, *J* = 7,8 Hz), 7,41 (1H, dd, *J* = 8,2, 2,5 Hz), 7,34 (1H, t, *J* = 7,7 Hz), 7,38 (1H, s), 7,18 (1H, d, *J* = 8,1 Hz), 6,62 (1H, d, *J* = 8,3 Hz), 4,51 (2H, t, *J* = 6,7 Hz), 3,70 (3H, s), 3,28 (3H, s), 2,96 (2H, t, *J* = 6,8 Hz), 2,95 (1H, d, *J* = 13,9 Hz), 2,86 (1H, d, *J* = 13,9 Hz), 2,32 (3H, s), 1,32 (3H, s)	para BR 429 $(M+H)^+$

d-38		($CDCl_3$, 400 MHz) 7,91 (1H, d, J = 2,0 Hz), 7,41 (1H, dd, J = 8,5, 2,4 Hz), 7,34-7,29 (2H, m), 6,96-6,93 (2H, m), 6,62 (1H, d, J = 8,5 Hz), 4,52 (2H, t, J = 6,8 Hz), 3,70 (3H, s), 3,28 (3H, s), 2,96 (2H, t, J = 6,8 Hz), 2,95 (1H, d, J = 13,9 Hz), 2,86 (1H, d, J = 13,9 Hz), 2,32 (3H, s), 2,16 (3H, s), 1,32 (3H, s)	para BR 441 $(M+H)^+$

Los compuestos de la invención se han ensayado para actividades frente a PPAR gamma y PPAR alfa. Las actividades se tabulan más adelante en Ki (µm)

Ejemplo nº	PPAR gamma Ki (µm)	PPAR alfa Ki (µm)	Ejemplo nº	PPAR gamma Ki (µm)	PPAR alfa Ki (µm)	Ejemplo nº	PPAR gamma Ki (µm)	PPAR alfa Ki (µm)
A – 02		0,55	B – 02		2,2	C – 03		2,9
A – 03	10	19	B – 03	31	9	C – 05		15
A – 05 E/M	0,33	2,6	B – 04	1,5	48	C – 06	9,5	41
A – 05 S/E	3,4	7,5	B – 05	1,33	2,04	C – 07	11	22
A – 05 S/E	0,19	1,1	B – 05	2,9	3,2	C – 09	1,4	4,6
A – 07		0,12	B – 05	2	3,6	C – 10	2,1	19
A – 10	1,5	4,4	B – 06	0,37	0,13	C – 11	2	25

Ejemplo nº	PPAR gamma KI (µm)	PPAR alfa KI (µm)	Ejemplo nº	PPAR gamma KI (µm)	PPAR alfa KI (µm)	Ejemplo nº	PPAR gamma KI (µm)	PPAR alfa KI (µm)
A – 11	0,58	0,12	B – 07	0,65	12	C – 12	1,6	9,4
A – 12	0,051	0,35	B – 08	0,48	3,1	C – 14	8	3,2
A – 13	3,5	10	B – 09	1,9	2,2	C – 15	14	3,2
A – 14	1,3	0,15	B – 10	0,17	0,19	C – 17	26	3,2
A – 15	1,2	0,16	B – 11	7,9	0,96	C – 18	3,5	0,065
A – 16	2,8	1,5	B – 12	33	0,3	C – 20	1,5	3,1
A – 17	1,9	1,6	B – 13		9	C – 21	0,053	0,066
A – 18	1,7	14	B – 14	2,3	0,021	C – 22	0,8	2,1
A – 19	0,059	0,7	B – 16	1,8	0,084	C – 23	0,19	2,5
A – 20	0,18	0,14	B – 17	1,2	0,047	C – 24	0,083	0,022
A – 21	0,088	0,31	B – 18		0,082	C – 25	0,066	0,018
A – 22	0,17	0,85	B – 19	0,74	0,34	C – 26	0,068	0,016
A – 23	0,39	0,18	B – 20		1,6	C – 27	0,026	0,015
A – 24	0,78	0,018	B – 21	0,99	4	C – 28	0,03	0,088
A – 25	3,2	4,2	B – 22	0,15	0,46	C – 29	0,006	0,12
A – 26	0,15	0,33	B – 23	3,4	2,7	C – 30	0,033	0,11
A – 27	2,4	1,3	B – 24	1,6	1	C – 31	0,026	0,093
A – 28 E/M	0,044	0,93	B – 27		0,22	C – 32	0,035	0,15
A – 28 S/E	0,081	1,1	B – 28		7,8	C – 33	0,05	0,01
A – 28 S/E	0,94	2,9	C – 02		0,39	C – 36	1,7	21

E/M se define como mezcla enantiomérica, incluyendo mezcla racémica.

S/E se define como enantiómero individual.

Ejemplo nº	PPAR gamma KI (µm)	PPAR alfa KI (µm)	Ejemplo nº	PPAR gamma KI (µm)	PPAR alfa KI (µm)	Ejemplo nº	PPAR gamma KI (µm)	PPAR alfa KI (µm)
C – 38	7,2		C – 64	0,052	0,014	C – 90	0,017	0,11
C – 40	3,7	0,7	C – 66	0,023	0,031	C – 91	0,39	1,8
C – 42	33	13	C – 67	0,044	0,25	C – 92	1,1	2,8
C – 44		36	C – 68	4,2		C – 93	0,011	0,3
C – 45	0,22	7,7	C – 69	1,1	2,5	C – 94	7	
C – 46	2	3,5	C – 70		6,4	C – 95	0,97	8,6
C – 47	3,5	8,3	C – 71		9,7	D – 02	0,46	0,29
C – 48	0,018	0,24	C – 72		7,1	D – 03	0,011	0,3
C – 48 E/M	0,15	0,31	C – 73	0,042		D – 04	0,44	0,29
C – 48 S/E	0,014	0,047	C – 74	0,64	0,9	D – 05	2,8	
C – 48 S/E		2,4	C – 74 S/E			D – 06	0,027	0,13
C – 49	0,21	1,6	C – 74 S/E	0,47	4,2	D – 07	0,017	0,32
C – 49	21	41	C – 75	0,82		D – 08	0,002	0,015
C – 49	0,043	0,34	C – 76	2,3	7,3	D – 09	0,061	0,05
C – 50	0,043	1,1	C – 77	0,15	2,9	D – 10	0,019	0,033
C – 51	0,18	2,9	C – 78	0,006	0,015	D – 11	6,2	5,1

Ejemplo nº	PPAR gamma Ki (µm)	PPAR alfa Ki (µm)	Ejemplo nº	PPAR gamma Ki (µm)	PPAR alfa Ki (µm)	Ejemplo nº	PPAR gamma Ki (µm)	PPAR alfa Ki (µm)
C – 52	0,3	0,15	C – 78 S/E	3,9		D – 12	8,1	
C – 53	0,093	0,64	C – 78 S/E	0,003	0,014	D – 13	0,36	0,19
C – 53 S/E	3,6		C – 79	0,007	0,015	D – 14	1,5	2,6
C – 53 S/E	0,027	0,4	C – 80	0,062	0,053	D – 15	0,35	0,22
C – 54	0,02	1,2	C – 81	0,015	0,75	D – 16	6,4	
C – 55	6		C – 82	0,016		D – 17	0,031	0,91
C – 56	0,081	0,078	C – 83	0,008	0,004	D – 18	0,45	0,62
C – 57	1,1	1,8	C – 84	0,021	0,064	D – 19	1,7	6,4
C – 59	0,009	0,054	C – 85	0,004	0,013	D – 20	0,48	0,84
C – 60	0,015	0,065	C – 86	0,005	0,013	D – 21	2,1	10
C – 61	0,31	0,24	C – 87	0,012	0,025	D – 23 E/M	0,073	6,5
C – 63	0,094	0,021	C – 89	0,04	0,03	D – 23 S/E	5	

E/M se define como mezcla enantiomérica, incluyendo mezcla racémica.

S/E se define como enantiómero individual.

Ejemplo nº	PPAR gamma Ki (µm)	PPAR alfa KI (µm)	Ejemplo nº	PPAR gamma KI (µm)	PPAR alfa Ki (µm)
D – 23 S/E	0,039	1,1	D – 33	0,69	0,55
D – 24	sin SPA	sin SPA	D – 34	9,1	3,2
D – 24	0,58	0,93	D – 35	0,56	0,33
D – 25	2,9		D – 35 S/E	0,27	0,57
D – 26	sin SPA	sin SPA	D – 35 S/E	4,8	9
D – 26 S/E	1,9		D – 36	0,23	0,73
D – 26 S/E	0,042	0,67	D – 37	0,53	4,7
D – 27	7,8		D – 38	9,6	
D – 28	1,6	4,8	D – 39	5	
D – 29	0,4	0,8	D – 40	9,6	1,8
D – 29 S/E	1,2		D – 41		5,9
D – 29 S/E	0,69	3	D – 42	0,7	1
D – 31	1	0,088	D – 44	0,15	2,6
D – 32	1,5	0,059	D – 45	0,058	0,09

E/M se define como mezcla enantiomérica, incluyendo mezcla racémica.

S/E se define como enantiómero individual.

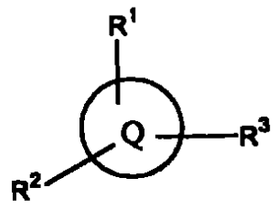
Aunque la invención se ha ilustrado mediante referencia a realizaciones específicas y preferidas, los expertos en la técnica reconocerán que se pueden hacer variaciones y modificaciones mediante experimentación rutinaria y práctica de la invención. Así que, no se pretende limitar la invención por la descripción anterior, sino que se define mediante las reivindicaciones anexas y sus equivalentes.

Habiendo descrito la invención como antecede se declara como propiedad lo contenido en las siguientes

REIVINDICACIONES

Los autores reivindican

1. Un compuesto de fórmula (I):



o una sal o solvato farmacéuticamente aceptable del mismo, en la que :

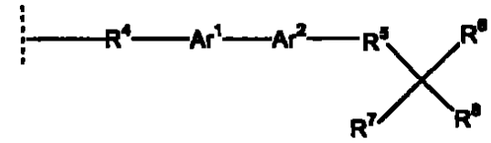
el anillo Q es arilo ($C_6 - C_{10}$) o heterociclilo de (4 – 10) eslabones;

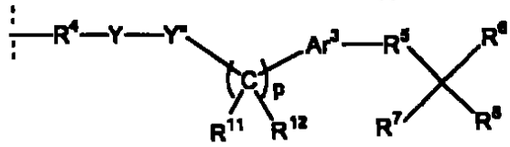
R^1 es H, halo, alquilo ($C_1 - C_8$), alcoxi ($C_1 - C_8$), CN, CF_3, -O-CF_3, -O-SO_2-alquilo ($C_1 - C_8$), –O-SO_2–$(CR^{11}R^{12})_t$ arilo ($C_6 - C_{10}$), –$(CR^{11}R^{12})_t$ cicloalquil ($C_3 - C_{10}$) – $(CR^{11}R^{12})_t$, –$(CR^{11}R^{12})_t$ cicloalquil ($C_3 - C_{10}$) – $(CR^{11}R^{12})_t$– O –, – $(CR^{11}R^{12})_t$ aril ($C_6 - C_{10}$) – $(CR^{11}R^{12})_t$, –$(CR^{11}R^{12})_t$ aril ($C_6 - C_{10}$)$_t$ - $(CR^{11}R^{12})_t$- O –, –$(CR^{11}R^{12})_t$ heterociclil de (4 – 10) eslabones – $(CR^{11}R^{12})_t$, o – $(CR^{11}R^{12})_t$ heterocoiclil de (4 – 10) eslabones – $(CR^{11}R^{12})_t$ –O–; en el que los átomos de carbono del anillo R^1 están opcionalmente sustituidos por 1 a 3 grupos R^{13}; y los átomos de nitrógeno en el anillo de R^1 están opcionalmente sustituidos con 1 a 3 alquilo ($C_1 - C_8$);

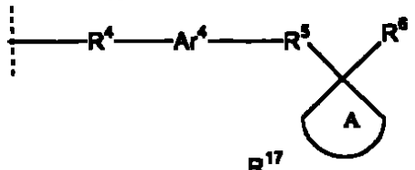
R^2 es H, alquilo ($C_1 - C_8$), –$(CR^{11}R^{12})_t$ – cicloalquilo ($C_3 - C_{10}$), – $(CR^{11}R^{12})_t$ – arilo ($C_6 - C_{10}$) o – $(CR^{11}R^{12})_t$ heterociclilo de (4 – 10) eslabones; y

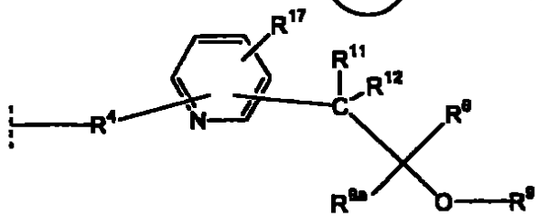
en el que los átomos de carbono de R^2 están opcionalmente sustituidos con 1 a 3 grupos R^{13}; y los átomos de nitrógeno en el anillo de R^2 están opcionalmente sustituidos con 1 a 3 alquilo ($C_1 - C_8$);

R^2 se selecciona entre el grupo constituido por:

A) 
;

B) 
;

C) 
; y

D) 
;

Y es –(C=O) – o –SO_2–;

Y" es NR^{10} u –O–;

p es 0, 1, ó 2;

cada q, r, y t son independientemente 0, 1, 2, 3, 4, ó 5;

cada n es independientemente 0, 1, 2, 3 ó 4;

cada k es independientemente 1, 2 ó 3;

cada m y s son independientemente 0, 1, 2, ó 3;

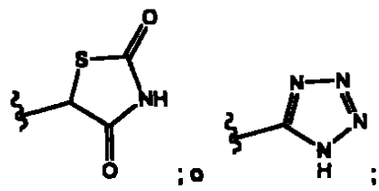
cada j es 0, 1, ó 2;

Cada R^4 es $-(CR^{11}R^{12})_n-$, $-(CR^{11}R^{12})_n-S-(CR^{11}R^{12})_n-$, $-(CR^{11}R^{12})_n-$

NR^{10}–, –$(CR^{11}R^{12})_n$ –NR^{10}– $(CR^{11}R^{12})_n$ –O–, –$(CR^{11}R^{12})_n$–O–$(CR^{11}R^{12})_k$ – NR^{10}, –$(CR^{11}R^{12})_n$–O–$(CR^{11}R^{12})_n$–, –$(CR^{11}R^{12})_n$–O–$(CR^{11}R^{12})_k$–O–$(CR^{11}R^{12})_n$–, – $(CR^{11}R^{12})_n$ –CR^{11}= CR^{12} – $(CR^{11}R^{12})_n$–, o –CH=CH–$(CR^{11}R^{12})$ –O– $(CH_2)_n$–;

Cada R^5 es un enlace o –$(CR^{11}R^{12})_m$– Z –$(CR^{11}R^{12})_s$; en el que Z es – $CR^{11}R^{12}$–, –O–NR^{10a} –, o –$(SO)_t$;

Cada R^6 es –(C=O)–OH, –(C=O)–OM^+, –(C=O) – alquilo (C_1 – C_8), – (C=O) – O – alquilo (C_1 – C_8), –(C=O)–$NR^{10}R^{11}$, –(C=O)–NR^{10} – SO_2 – R^{11}, – SO_2 – NH – R^{10}, – NH – SO_2 –R^{10}, –(C=O) – NH – C ≡ N, o R^6 tiene una fórmula:



;

M^+ es un catión de metal alcalino o un catión de metal alcalinotérreo;

Cada R^7 y R^8 es independientemente H, alquilo (C_1 – C_8), alcoxi (C_1 – C_8), – $(CR^{11}R^{12})_t$ cicloalquilo (C_3 – C_{10}), –$(CR^{11}R^{12})_t$ arilo (C_6 – C_{10}), –$(CR^{11}R^{12})_t$ aril (C_6 – C_{10}) –O–, –$(CR^{11}R^{12})_t$ heterococlilo de (4 – 10) eslabones o – $(CR^{11}R^{12})_t$ heterociclil de (4 – 10) eslabones –O–;

O R^7 y R^8 pueden opcionalmente tomarse juntos con el carbono al que están unidos para formar un cicloalquilo (C_3 – C_{10}) o un heterociclilo de (3 – 10) eslabones;

Cada Ar^1, Ar^2, Ar^3, y Ar^4 representa arilo (C_6 – C_{10}) o heterociclilo (5 – 10) eslabones; en el que los átomos de carbono en el anillo de cada Ar^1, Ar^2, Ar^3, y Ar^4 están opcionalmente sustituidos con uno a tres grupos R^{13};

El anillo A representa un anillo de 3, 4, 5, 6 ó 7 eslabones conteniendo opcionalmente 1 a 4 heteroátomos que pueden ser el mismo o diferente y que se seleccionan entre $-N(R^{10a})-$, O, y $S(O)_j$, en el que j es 0, 1, ó 2, con la condición de que el anillo no contenga dos átomos de O o $S(O)_j$ adyacentes, y en el que los átomos de carbono del resto A en el anillo estén opcionalmente sustituidos con uno a tres grupos R^{13};

R^9 es alquilo ($C_1 - C_8$), $-(CR^{11}R^{12})_t$ – arilo ($C_6 - C_{10}$) o $(CR^{11}R^{12})_t$ – heterociclilo de (4 – 10) eslabones, en los que t es independientemente 0, 1, 2, 3, 4, ó 5, en el que dichos grupos R^9 están sustituidos con 1 a 3 grupos independientemente seleccionados entre $-(CR^{11}R^{12})_qNR^{10}R^{11}$, $-(CR^{11}R^{12})_qNR^{10}$ alcanoílo ($C_1 - C_8$), $-(CR^{11}R^{12})_qO(CR^{11}R^{12})_rR^{10}$, y $-(CR^{11}R^{12})_qR^{10}$; y en el que los restos heterociclilo, arilo y alquilo de los grupos anteriores están opcionalmente sustituidos con uno a tres grupos R^{13};

R^{9a} y R^{10} son independientemente H o alquilo ($C_1 - C_8$);

R^{11} y R^{12} son independientemente H, alquilo ($C_1 - C_8$), hidroxi, o alcoxi ($C_1 - C_8$);

R^{10a} se selecciona entre H, alquilo ($C_1 - C_8$), $-(C=O)-R^{14}$, $-SO_2NR^{15}R^{16}$, o $-(SO)_j$ alquilo ($C_1 - C_8$);

Cada R^{13} y R^{13a} se seleccionan independientemente entre el grupo constituido por halo, ciano, nitro, trifluorometoxi, trifluorometilo, azido, hidroxi, alcoxi ($C_1 - C_8$), alquilo ($C_1 - C_{10}$), alquenilo ($C_2 - C_8$), alquinilo ($C_2 - C_8$), $-O-(CR^{11}R^{12})_k-O-(CR^{11}R^{12})_n-$, $-(C=O)-R^{14}$, $-(C=O)-O-R^{15}$, $-O-(C=O)-R^{15}$, $-NR^{15}(C=O)-R^{16}$, $-NR^{15}(C=O)-O-R^{16}$, $-(C=O)-NR^{15}R^{16}$, $-NR^{15}R^{16}$, $-NR^{15}OR^{16}$, $-SO_2R^{15}R^{16}$, $-S(O)_j$ alquilo ($C_1 - C_8$), $-O-SO_2-R^{14}$, $-NR^{15}-SO_2-R^{16}$, $R^{15}-(CR^{11}R^{12})_t-$arilo ($C_6 - C_{10}$), $-(CR^{11}R^{12})_t$ heterociclilo de (4 – 10) eslabones, –

$(CR^{11}R^{12})_q(C=O)$ $(CR^{11}R^{12})_t$ arilo $(C_6 - C_{10})$, $-(CR^{11}R^{12})_q(C=O)(CR^{11}R^{12})_t$ heterociclilo de (4 – 10) eslabones, $-(CR^{11}R^{12})_tO(CR^{11}R^{12})_q$ arilo $(C_6 - C_{10})$, $-(CR^{11}R^{12})_tO(CR^{11}R^{12})_q$ heterociclilo de (4 – 10) eslabones, $-(CR^{11}R^{12})_qSO_2$ $(CR^{11}R^{12})_t$ arilo $(C_6 - C_{10})$, y $-(CR^{11}R^{12})_qSO_2$ $(CR^{11}R^{12})_t$ heterociclilo de (4 – 10) eslabones; 1 ó 2 átomos de carbono en el anillo de los restos heterocíclicos de los grupos anteriores R^{13} y R^{13a} están opcionalmente sustituidos con un resto oxo (=O), y los restos alquilo, alquenilo, alquinilo, arilo y heterocíclicos de los grupos anteriores R^{13} y R^{13a} están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente entre halo, ciano, nitro, trifluorometilo, trifluorometoxi, azido, $-OR^{15}$, $-(C=O)-R^{15}$, $-(C=O)-O-R^{15}$, $-O-(C=O)-R^{15}$, $-NR^{15}(C=O)-R^{16}$, $-(C=O)-NR^{15}R^{16}$, $-NR^{15}R^{16}$, $-NR^{15}OR^{16}$, alquilo $(C_1 - C_6)$, alquenilo $(C_2 - C_6)$, alquinilo $(C_2 - C_6)$, $-(CR^{11}R^{12})_t$ arilo $(C_6 - C_{10})$, y $-(CR^{11}R^{12})_t$ heterociclilo de (4 – 10) eslabones;

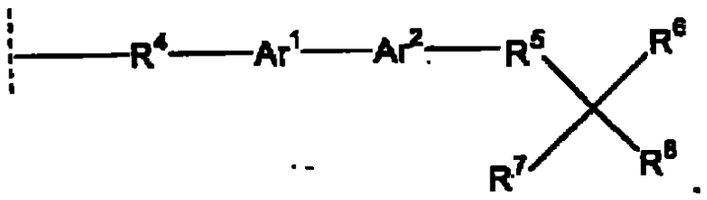
cada R^{14}, R^{15}, y R^{16} se selecciona independientemente entre H, alquilo $(C_1 - C_6)$, $-(CR^{11}R^{12})_t$ arilo $(C_6 - C_{10})$ y $-(CR^{11}R^{12})_t$ heterociclilo de (4 – 10) eslabones; 1 ó 2 átomos de carbono en el anillo del grupo heterocíclico están opcionalmente sustituidos con un resto oxo (=O), y los retos, alquilo, arilo y heterocíclicos de los grupos anteriores R^{14}, R^{15} y R^{16} están opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados independientemente entre halo, ciano, nitro, $-NR^{11}R^{12}$, trifluorometilo, trifluorometoxi, alquilo $(C_1 - C_6)$, alquenilo $(C_2 - C_6)$, alquinilo $(C_2 - C_6)$, hidroxi, y alcoxi $(C_1 - C_6)$;

R^{17} es H, alquilo $(C_1 - C_6)$, –O– alquilo $(C_1 - C_6)$, halo, CN, OH, CF_3, o $-O-CF_3$;

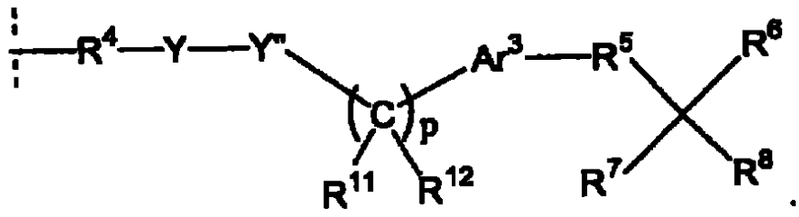
y en el que cualquiera de los sustituyentes anteriormente mencionados comprenden un grupo CH_3 (metilo), CH_2 (metileno), o CH (metino) que no está

unido a un grupo halo, SO o SO_2 o a un átomo N, O o S opcionalmente se soporta sobre dicho grupo un sustituyente seleccionado entre hidroxi, halo, alquilo ($C_1 - C_4$), alcoxi ($C_1 - C_4$), $-NH_2$, –NH alquilo ($C_1 - C_8$), y –N(alquilo ($C_1 - C_8$))$_2$.

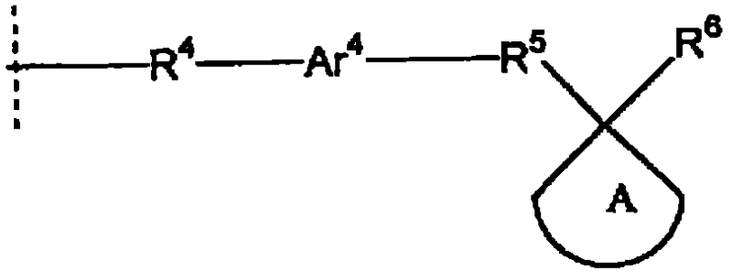
2. El compuesto según la reivindicación 1 en el que R^3 es

A) 

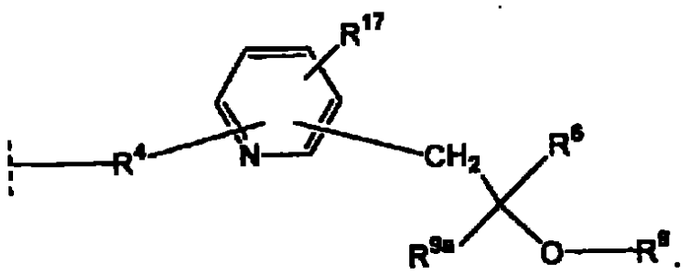
3. El compuesto según la reivindicación 1 en el que R^3 es

B) 

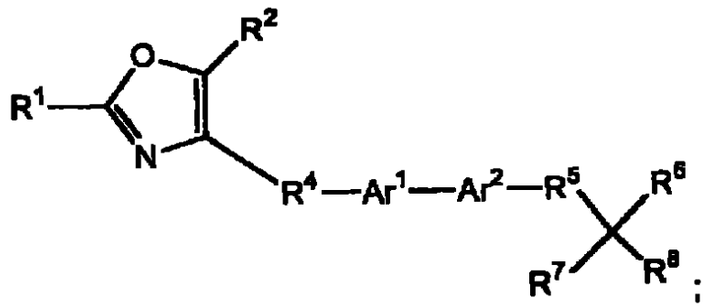
4. El compuesto según la reivindicación 1 en el que R^3 es

C) 

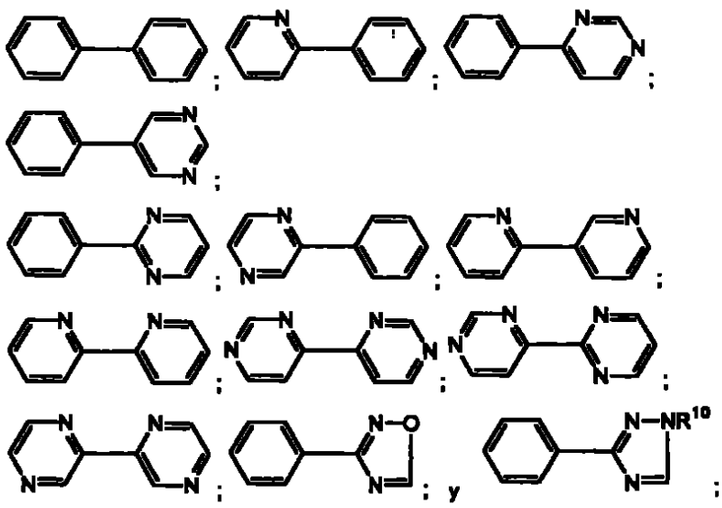
5. El compuesto según la reivindicación 1 en el que R^3 es

D) 

6. El compuesto según la reivindicación 2 que tiene una fórmula



en la que dicho $-Ar^1-Ar^2-$ se selecciona del grupo constituido por:



en las que los átomos de carbono en el anillo de cada Ar^1 y Ar^2 están opcionalmente sustituidos con 1 a 3 grupos R^{13} seleccionados entre el grupo constituido por halo, alquilo ($C_1 - C_8$) y alcoxi ($C_1 - C_8$).

7. El compuesto según la reivindicación 2 seleccionado entre el grupo constituido por

Ácido 1-({3'-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]-1,1'-bifenil-3-il}oxi)ciclobutanocarboxílico (ejemplo A – 4);

Ácido 2-({3'-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]-1,1'-bifenil-3-il}oxi)butanoico (ejemplo A – 5);

Ácido 2-(3-{6-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridin-2-il}fenoxi)butanoico (ejemplo A – 6);

Ácido 1-(3-{6-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridin-2-il}fenoxi) ciclobutanocarboxílico (ejemplo A – 7);

Ácido 1-[(3'-{[2-(3-fluorofenil)-5-metil-1,3-oxazol-4-il]metoxi}bifenil-3-il)oxi]ciclobutanocarboxílico (ejemplo A – 11);

Ácido 1-[(3'-[3-(5-metil-2-fenil-1,3-oxazol-4-il)propoxi]bifenil-3-il}oxi) ciclobutanocarboxílico (ejemplo A – 12);

Ácido 1-[(3'-{[5-(4-metoxifenil)-1,2,4-oxadiazol-3-il]metoxi}bifenil-3-il)oxi] ciclobutanocarboxílico (ejemplo A – 17);

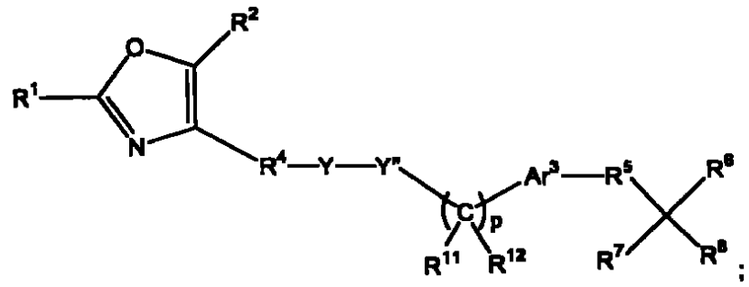
Ácido 2-[(3'-{2-[2-(3-fluorofenil)-5-metil-1,3-oxazol-4- il]etoxi}bifenil-3-il)oxi]-2-metilpropanoico (ejemplo A – 21);

Ácido 2-metil-2-({3'-[(5-metil-2-fenil-1,3-oxazol-4-il)metoxi]bifenil-3-il}oxi)propanoico (ejemplo A – 24);

Ácido 2-etoxi-3-[3'-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]bifenil-3-il}propanoico (ejemplo A – 28);

y las sales farmacéuticamente aceptables de los mismos.

8. El compuesto según la reivindicación 3 que tiene una fórmula



en la que Y es –(C=O) – o –SO_2–; Y" es NR^{10} y p es 1.

9. El compuesto según la reivindicación 3 seleccionado entre el grupo constituido por

Ácido 2-metil-2-{3-[({[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]carbonil}amino)metil]fenoxi}propanoico (ejemplo B – 5);

Ácido 2-metil-2-{3-[({[(5-metil-2-fenil-1,3-oxazol-4-il)metoxi]carbonil}amino)metil]fenoxi}propanoico (ejemplo B – 6);

Ácido 2-metil-2-{4-[({[3-(5-metil-2-fenil-1,3-oxazol-4-il)propoxi]carbonil}amino)metil]fenoxi}propanoico (ejemplo B – 7);

Ácido 2-{3-fluoro-4-[({[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]carbonil}amino)metil]fenoxi}-2-metilpropanoico (ejemplo B – 9);

Ácido 2-{3-[({[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]carbonil}amino)metil]fenoxi}butanoico (ejemplo B – 13);

Ácido 2-{3-[({[(5-metil-2-fenil-1,3-oxazol-4-il)metoxi]carbonil}amino)metil]fenoxi}butanoico (ejemplo B – 14);

Ácido 1-{3-[({[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]carbonil}amino)metil]fenoxi}ciclobutanocarboxílico (ejemplo B – 15);

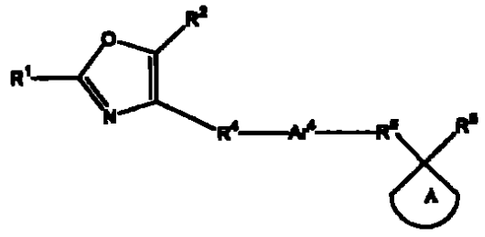
Ácido 2-metil-2-(3-{[({[2-(5-metil-2-fenil-1,3-oxazol-4-il)etil]amino}carbonil)oxi]metil}fenoxi)propanoico (ejemplo B – 21);

Ácido 2-etoxi-3-{3-[({[3-(5-metil-2-fenil-1,3-oxazol-4-il)propoxi]carbonil}amino)metil]fenil}propanoico (ejemplo B – 23);

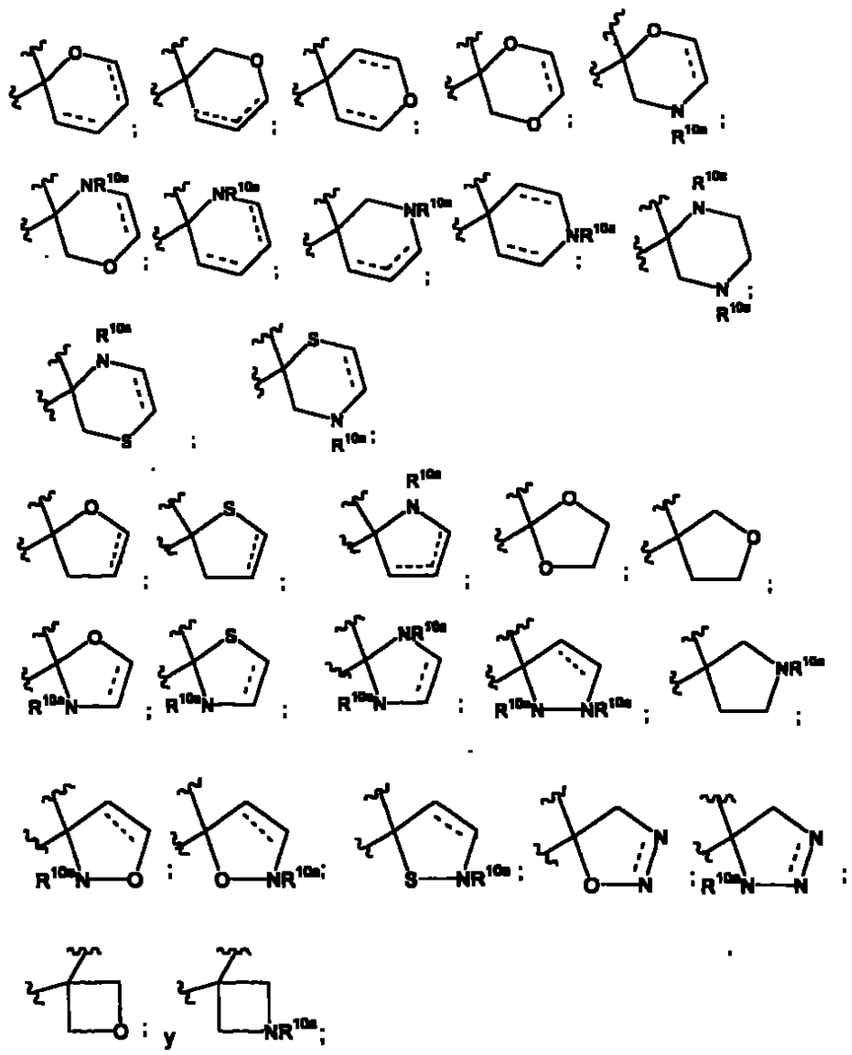
Ácido 2-etoxi-3-{3-[({[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]caboníl}amino)metil]fenil}propanoico (ejemplo B – 24);

y las sales farmacéuticamente aceptables de los mismos.

10. El compuesto según la reivindicación 4 que tiene una fórmula



en la que dicho anillo A se selecciona entre el grupo constituido por ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo,



en las que — es un doble enlace opcional.

11. El compuesto según la reivindicación 4 seleccionado entre el grupo constituido por

Ácido 1-{4-[3-(5-metil-2-fenil-1,3-oxazol-4-

il)propoxi]bencil}ciclobutanocarboxílico (ejemplo C – 16);

Ácido 1-{4-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]bencil}ciclobutanocarboxílico (ejemplo C – 19);

Ácido 2-({6-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridin-3-il}metil)tetrahidrofuran-2-carboxílico (ejemplo C – 48);

Ácido 2-({5-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridin-2-il}metil)tetrahidrofuran-2-carboxílico (ejemplo C – 49);

Ácido 2-({6-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridin-3-il}metil)tetrahidro-2*H*-piran-2-carboxílico (ejemplo C – 56);

Ácido 2-[(6-{2-[2-(3-clorofenil)-5-metil-1,3-oxazol-4-il)etoxi}piridin-3-il)metil]tetrahidrofuran-2-carboxílico (ejemplo C – 59);

Ácido 2-[(6-{2-[2-(3-metoxifenil)-5-metil-1,3-oxazol-4-il]etoxi}piridin-3-il)metil]tetrahidrofuran-2-carboxílico (ejemplo C – 62);

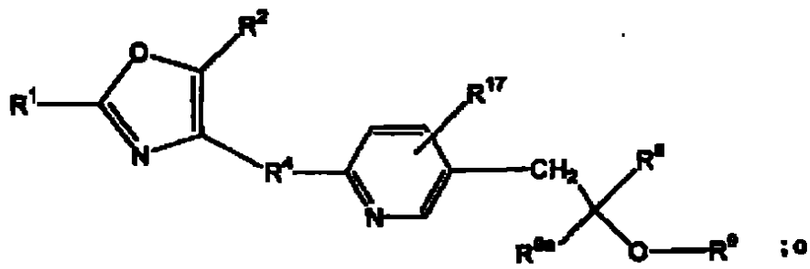
Ácido 2-{5-[2-(5-metil-2-feniloxazol-4-il)etoxi]pirazil-2-ilmetil}tetrahidrofuran-2-carboxílico (ejemplo C – 77);

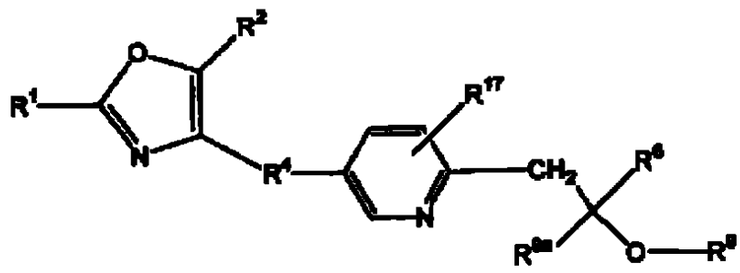
Ácido -{4-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]bencil}tetrahidrofuran-2-carboxílico (ejemplo C – 78);

Ácido 2-{6-[2-(5-metil-2-fenil-oxazol-4-il)etoxi]naftalen-2-ilmetil}tetrahidrofuran-2-carboxílico (ejemplo C – 91);

o las sales farmacéuticamente aceptable del mismo.

12. El compuesto según la reivindicación 5 que tiene una fórmula





13. El compuesto según la reivindicación 12 seleccionado entre el grupo constituido por

Ácido 2-etoxi-3-{6-[2-(5-metil-2-fenil-1,3-oxazol-4-il)etoxi]piridin-3-il}propanoico (ejemplo D – 1);

Ácido 2-metoxi-3-(6-{2-[5-metil-2-(3-metilfenil)-1,3-oxazol-4-il]etoxi}piridin-3-il)propanoico (ejemplo D – 3);

Ácido 2-metoxi-3-{6-[2-(4-fenoxifenil)etoxi]piridin-3-il}propanoico (ejemplo D – 13);

Ácido 2-etoxi-3-[6-{4-[(fenilsulfonil)oxi]fenil}etoxi)piridin-3-il]propanoico (ejemplo D – 17);

Ácido 2-etoxi-3-{5-[2-(5-metil-2-feniloxazol-4-il)etoxi]piridin-2-il}propiónico (ejemplo D – 23);

Ácido 2-metoxi-2-metil-3-{6-[3-(5-metil-2-feniloxazol-4-il)propoxi]piridin-3-

il}propiónico (ejemplo D – 27);

Ácido 2-metoxi-2-metil-3-{5-[2-(5-metil-2-feniloxazol-4-il)etoxi]piridin-2-il}propiónico (ejemplo D – 29);

Ácido 3-(6-{2-[2-(4-clorofenil)-5-metiloxazol-4-il)etoxi}piridin-3-il)-2-metoxi-2-metilpropiónico (ejemplo D – 30);

Ácido 2-metoxi-2-metil-3-{6-[2-(5-metil-2-feniloxazol-4-il)etoxi]piridin-3-il}propiónico (ejemplo D – 35);

Ácido 2-metoxi-3-(6-{2-[2-(3-metoxifenil)-5-metiloxazol-4-il]etoxi}piridin-3-il)-2-metilpropiónico (ejemplo D – 43);

o las sales farmacéuticamente aceptable del mismo.

14. Un procedimiento de tratamiento de diabetes mellitus no insulinodependiente, síndrome de ovario poliquístico, obesidad, hiperglucemia, hiperlipidemia, hipercolesteremia, aterosclerosis, hipertrigliceridemia, hiperinsulinemia, trastornos de insulina anormal y/o evidencia de glucosa, síndrome de resistencia a la insulina, y trastornos relativos a PPAR en un mamífero comprendiendo la administración a un mamífero necesitado de ello de una cantidad terapéuticamente eficaz de un compuesto ácido carboxílico alfasustituido según la reivindicación 1.

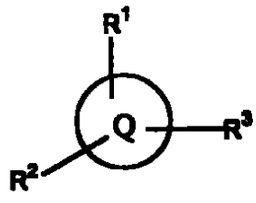
15. Una composición comprendiendo al menos un compuesto según la reivindicación 1 y un vehículo farmacéuticamente aceptable del mismo, dicho compuesto está opcionalmente en combinación con otros agentes tales como inhibidores de la α-glucosidasa, inhibidores de la

aldosarreductasa, preparaciones de biguanida, compuestos a base de estatina, inhibidores de la síntesis de escualeno, compuestos a base de fibratos, promotores del catabolismo de LDL e inhibidores de la enzima conversora de la angiotensina.

5

RESUMEN DE LA DESCRIPCIÓN

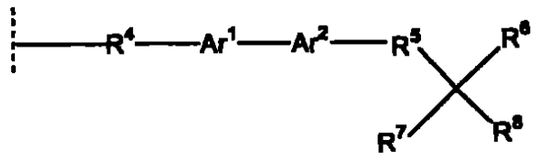
Ácidos carboxílicos alfasustituidos de fórmula (I):



(I);

en la que R^1 y R^2 son como se han definido en la memoria descriptiva y R^3 es

A)



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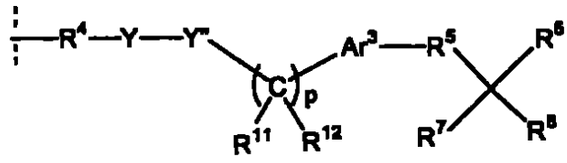
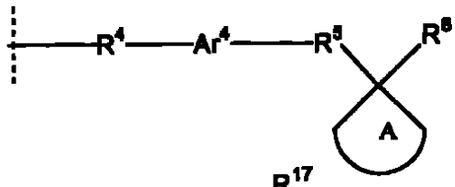
B)



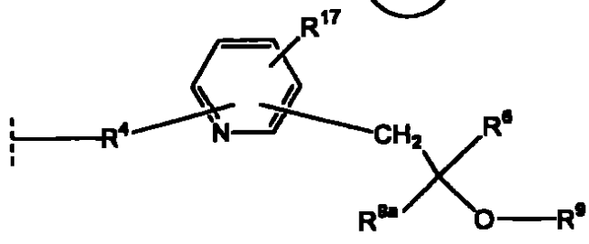
;

C)



; y

D)



;

en las que Y, Ar^1, Ar^2, Ar^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{9a}, R^{10}, R^{11}, R^{12}, R^{17}, anillo A, y p son como se han definido en la memoria descriptiva; las composiciones farmacéuticas conteniendo cantidades eficaces de dichos compuestos o sus sales son útiles para tratar PPAR, específicamente trastornos relacionados con PPAR α/γ, tales como diabetes, dislipidemia, obesidad y trastornos inflamatorios.

TRATADO DE COOPERACIÓN DE PATENTES
PCT
NOTIFICACIÓN DE TRANSMISIÓN DEL REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL
(PCT Regla 71.1)
De: AUTORIDAD DE REVISION PRELIMINAR INTERNACIONAL

Para:
WOOD, David J.
Pfizer Global Research and Developm
Ramsgate Road
Sandwich,
Kent CT13 9NJ
Gran Bretaña

Sello de de la Oficina de Patentes Europea Pharma 30 de agosto de 2005

Fecha de expedición: 26.08.2005
Referencia del expediente del solicitante o mandatario: PC25631A
Solicitud Internacional No.: PCT/IB2004/001159
Fecha de presentación internacional: 01.04.2004
Fecha de prioridad: 15.04.2003
Solicitante: PFIZER INC. et al

1. Se notifica al solicitante que la Administración Encargada del Examen Preliminar Internacional ha emitido el informe de examen preliminar internacional para la solicitud internacional y se lo transmite adjunto, acompañado, si procede, de sus anexos.

2. Se transmite una copia del presente informe y, si procede, de sus anexos, a la Oficina Internacional para comunicación a todas las Oficinas elegidas.

3. Si alguna Oficina elegida lo exige, la Oficina Internacional realizará una traducción en inglés del informe (con exclusión de sus anexos) y la transmitirá a las Oficinas interesadas.

4. **RECORDATORIO**

   Para iniciar la fase nacional ante cada Oficina elegida, el solicitante debe cumplir ciertos actos (presentación de la traducción y pago de las tasas nacionales) en el plazo de 30 meses desde la fecha de prioridad (o más tarde por lo que respecta a ciertas oficinas) (Artículo 39.1) (véase también el recordatorio enviado por la Oficina Internacional en el formulario PCT/IB/301).

Cuando deba entregarse una traducción de la solicitud internacional o una oficina elegida, se incluirá la traducción de cualquier anexo de informe de Examen Preliminar Internacional. Corresponde al solicitante preparar la traducción en cuestión y entregarla directamente a cada Oficina elegida interesada

Para más amplios detalles en lo relativo a los plazos aplicables y las exigencias de las oficinas elegidas, véase el Volumen II de la guía del solicitante PCT.

Se llama la atención del solicitante sobre el Artículo 33(5) que prevé que los criterios de novedad, actividad inventiva y de aplicación industrial definidos en el Artículo 33(2) a (4) sólo servirán a los efectos del examen preliminar internacional, y que "todo Estado contratante puede aplicar criterios adicionales o diferentes al objeto de decidir, en ese Estado, si la invención es patentable o no" (véase también el Artículo 27(5)). Tales criterios adicionales pueden afectar, por ejemplo, a las excepciones de patentabilidad, requisitos específicos relativos a la divulgación, la claridad de las reivindicaciones.

Nombre y dirección postal de la Administración encargada del Examen Preliminar Internacional:
Oficina de Patentes Europea –Gitschiner Str. 103
D-10958 – Berlín
Tel: +49-30 25901 - 0,
Fax: +49-30 25901-840.

Funcionario Autorizado: HALBARTSCHLAGER, M
Tel: + 49 30 25901-714

TRATADO DE COOPERACIÓN DE PATENTES
PCT
INFORME PRELIMINAR INTERNACIONAL SOBRE PATENTABILIDAD
(Capítulo II del Tratado de Cooperación en materia de Patentes)
(PCT Artículo 36 y Regla 70)

Referencia del expediente del solicitante o mandatario: PC25631A
Solicitud Internacional No.: PCT/IB2004/001159
Fecha de presentación internacional: 01.04.2004
Fecha de prioridad: 15.04.2003
Clasificación Internacional de Patentes (IPC) o la vez clasificación nacional e IPC: C07D263/00, C07D263/32
Solicitante: PFIZER INC. et al

1. El presente informe preliminar internacional sobre patentabilidad, se establece por esta Administración encargada del examen preliminar internacional según el Artículo 35 y se transmite al solicitante conforme el Artículo 36.

2. Este INFORME consta de un total de 6 hojas, incluida la presente hoja de portada.

3. Este informe también contiene ANEXOS, que comprenden.
   a. ☐ (*remitido al solicitante y a la oficina internacional*) un total de ___ hojas, descritas a continuación:
      ☐ hojas de la descripción, las reivindicaciones y/o los dibujos que han sido modificadas y que sirven de base al presente informe, y/o de hojas que contienen rectificaciones autorizadas por esta Administración (véase la Regla 70.16 y la Instrucción Administrativa 607 del PCT).

      ☐ hojas que reemplazan a otras hojas anteriores, pero que esta Administración considera que contienen modificaciones que se extienden más allá de la divulgación de la invención tal como fue originalmente presentada, según se indica en el punto 4 del Reglamento I y en el Recuadro Suplementario.

   b. ☐ (remitido únicamente a la Oficina Internacional) un total de (indicar tipo y soporte(s) electrónico(s)) , que contienen una lista de secuencias y/o tabla(s) relativa(s), solo en formato legible por ordenador, como se indica en el Recuadro Suplementario relativo a Listas de Secuencias (ver Instrucción Administrativa 802).

4. El presente informe contiene indicaciones relativas a los siguientes puntos:

☒	Recuadro I	Base de este informe
☐	Recuadro II	Prioridad
☒	Recuadro III	Ninguna formulación de opinión sobre la novedad, la actividad inventiva y la aplicación industrial
☐	Recuadro IV	Falta de unidad de Invención
☒	Recuadro V	Declaración motivada según el Artículo 35(2) sobre la novedad, la actividad inventiva y la aplicación industrial, citas y explicaciones en apoyo de esta declaración
☐	Recuadro VI	Ciertos documentos citados
☐	Recuadro VII	Defectos en la Solicitud Internacional
☐	Recuadro VIII	Observaciones relativas a la solicitud internacional

Fecha de radicación de la demanda: 30.04.2004
Fecha de elaboración de este reporte: 26.08.2005

Nombre y dirección postal de la Administración encargada del Examen Preliminar Internacional:
Oficina de Patentes Europea –Gitschiner Str. 103
D-10958 – Berlín
Tel: +49-30 25901 - 0,
Fax: +49-30 25901-840.

Funcionario Autorizado: Hoepfner, W.
Tel: + 49 30 25901-337

Recuadro I. Base de este informe

1. Por lo que respecta al **idioma**, este informe se ha establecido sobre la base de la solicitud internacional en el idioma en el cual se depositó, salvo indicación en contra señalada a continuación.

☐ Este informe está basado en una traducción del idioma original al siguiente idioma , que es el de una traducción proporcionada a los fines de:
- ☐ búsqueda internacional (según Reglas 12.3 y 23.1 (b))
- ☐ publicación de la solicitud internacional (según Regla 12.4)
- ☐ examen preliminar internacional (según Reglas 55.2 y/o 55.3)

2. Por lo que respecta a los **elementos** de la solicitud internacional, esta opinión se ha establecido sobre la base de (*las hojas de reemplazo que hayan sido enviadas a la Oficina receptora en respuesta a un requerimiento según el Artículo 14 se las denomina en este informe como "inicialmente presentadas" y no se anexan al informe):*

Descripción, Páginas

1 – 162 tal como se presentaron inicialmente

Reivindicaciones, Números

1 – 15 tal como se presentaron inicialmente

☐ una lista de secuencias y/o tabla(s) relativa(s) – ver Recuadro Suplementario relativo a Listas de Secuencias

3. Las modificaciones ha ocasionado la cancelación de:

- ☐ la descripción, páginas
- ☐ las reivindicaciones, Nos.
- ☐ los dibujos, hojas/fig.
- ☐ la lista de secuencias (especificar):
- ☐ tabla(s) relativa(s) a la lista de secuencias (especificar):

4. ☐ El presente informe ha sido establecido como si no se hubiesen presentado (algunas de) las modificaciones anexadas a este informe y listadas abajo, ya que se ha considerado que iban más allá de la divulgación de la invención tal como fue presentada, como se indica en el Recuadro Suplementario (Regla 70.2(c)).

☐ la descripción, páginas
☐ las reivindicaciones, Nos.
☐ los dibujos, hojas/fig.
☐ la lista de secuencias (especificar):
☐ tabla(s) relativa(s) a la lista de secuencias (especificar):

* Si se utiliza el punto 4, algunas o todas estas páginas pueden llevar el sello de "sustituida".

Recuadro No. III. Ninguna formulación de opinión sobre la novedad, la actividad inventiva y la aplicación industrial

1. Las preguntas con respecto a si el invento reivindicado parece ser novedoso, implica una actividad inventiva (no ser evidente), o ser susceptible de aplicación industrial, por lo que respecta.

☐ al conjunto de la solicitud internacional,
☒ a las reivindicaciones Nos. 1-13, 15 (con respecto al nivel inventivo), 14 (con respecto a nivel inventivo y aplicación industrial)

debido a que:

☒ la solicitud internacional, o las reivindicaciones Nos. 1-15 en cuestión se refieren al objeto, respecto del cual no requiere examen preliminar internacional (especifique):

ver hoja separada

☐ a descripción, reivindicaciones, o los dibujos (indíquese cuales a continuación) o tales reivindicaciones Nos. en cuestión no son claras, de manera que no es posible formular una opinión significativa (especifique):

☐ las reivindicaciones, o las reivindicaciones Nos. en cuestión no son claras, de manera que no es posible formular una opinión significativa.

☐ no se ha emitido informe de búsqueda internacional para dichas reivindicaciones Nos.

☐ la lista de de secuencias nucleótidas y/o de aminoácidos no cumplen la norma estándar prevista en el Anexo C de las Instrucciones Administrativas por que:

La lista en papel ☐ no se presentó

☐ no cumple con la norma estándar

La lista en formato legible por ordenador

☐ no se presentó

☐ no cumple con la norma estándar

☐ las tablas relativas a las listas de secuencias de nucleótidas y/o de aminoácidos, si únicamente se han presentado en formato legible por ordenador, no cumplen con los requisitos técnicos previstos en el Anexo C-*bis* de las Instrucciones Administrativas.

☐ Ver recuadro suplementario para más detalles.

Recuadro No. V Declaración razonada según el Artículo 35(2) con respecto a la novedad, nivel inventivo o aplicación industrial: anterioridades y explicaciones que soportan tal declaración

---

1. Declaración

Novedad (N)	Si:	Reivindicaciones 2, 4-7, 10-13
	No:	Reivindicaciones 1, 3, 8, 9, 14, 15
Nivel Inventivo (NI)	Si:	Reivindicaciones -
	No:	Reivindicaciones -
Aplicación Industrial (AI)	Si:	Reivindicaciones 1-13, 15
	No:	Reivindicaciones -

2. Citas y explicaciones (Regla 70.7)

ver hoja separada.

REPORTE DE EXAMEN PRELIMINAR INTERNACI NAL – HOJA ANEXA
Solicitud Internacional No. PCT/IB2004/001159

Re Sección III
No se establece opinión con respecto a novedad, nivel inventivo y aplicación industrial

La materia de las presentes reivindicaciones 1, 3, 8, 9, 14 y 15 no es considerada novedosa (ver parágrafo V abajo). Puesto que no es actualmente clara, en el cual posiblemente permanece la novedad, materia de la presente solicitud debe ser basada más a fondo, no se formulará ninguna opinión con respecto al nivel inventivo de cualquier materia actualizada de las reivindicaciones 1-15 (Artículo 34(4)(a)(ii) del PCT).

Aparte del precedente, se eleva la pregunta, si es posible que restableciendo la novedad de la materia podría encontrar en los requisitos de la Regla 13 del PCT en vista del citado arte previo (en particular D1; ver parágrafo V abajo), i.e. si materia semejante puede ser distinguida de dicho arte previo por medio de uno solo (unitario) distinguiendo el rasgo.

La reivindicación 14 relaciona la materia considerada por esta Autoridad cubierta por las provisiones establecidas en la Regla 67.1 (iv) del PCT. Por lo tanto, la Autoridad de Examen Internacional totalmente concurre con la objeción puesta adelante por la Autoridad de Búsqueda Internacional y no se formulará ninguna opinión con respecto a la aplicación industrial de la materia de esta reivindicación (Artículo 34(4)(a)(i) del PCT).

Re Sección V
Declaración razonada con respecto a novedad, nivel inventivo o aplicación industrial; citaciones y explicaciones que soportan dicha declaración.

D1: WO 02/064130 A (PFIZER PROD INC; HAYWARD CHERYL MYERS (US); PERRY DAVID AUSTEN (US)) 22 de agosto de 2002 (2002-08-22)

D2: EP-A-1 088 824 (PFIZER PROD INC) 4 de abril de 2001 (2001-04-04)

Novedad

La materia de la reivindicación 1 oculta con la materia de D1 ocultando las posiciones siendo Q=aril; Y= -(C=O)-, -SO_2-; Y^a= -$N(R^{10})$-, -O-; R^5= -$(CR^{11}R^{12})_m$-; R6= -COOH, -(C=O)-O-(C_1-C_8)alquil, -(C=O)-$NR^{10}R^{11}$, -

(C=O)-NR^{10}-SO_2-R^{11}, tetrazolil; R^7 = R^8 = R^{10} = R^{12} = H; R^{11}=H, OH; Ar^3=fenileno; p=2; n=1 (ver página 2, líneas 19-21; página 2 Fórmula I, pagina 16, líneas 18-22).

El documento D2 revela además compuestos usados en el tratamiento de diabetes (ver página 3 líneas 56-58; páginas 4, Fórmula I; página 18, líneas 14, 18-20).

En vista de esta anterioridad, parece que la materia independiente de las presentes reivindicaciones 1, 14 y 15 y las presentes reivindicaciones independientes 3, 8 y 9 carecen de novedad.

Aplicación Industrial

No hay ninguna duda que la materia que las presentes reivindicaciones 1-13 y 15 es industrialmente aplicable.
Sin embargo, para la evaluación de la reivindicación 14 de la presente, sobre si es industrialmente aplicable, no existen criterios unificados en los Estados pertenecientes al PCT. La patentabilidad también puede depender de la formulación de las reivindicaciones. La EPO, por ejemplo, no reconoce como industrialmente aplicable aquella materia que reivindique el uso de un compuesto en tratamiento médico, pero permite, sin embargo, reivindicar sobre un compuesto conocido para primero uso en tratamiento médico y el uso de tal compuesto en la manufactura de un medicamento para un nuevo tratamiento médico.

Las materias formales

Parece que la materia de las reivindicaciones 1-6, 8, 10 y 12 no está en línea con el título de la invención, desde que la definición del grupo R^6 comprende solo grupos funcionales de otra manera que ácidos carboxilicos o sus derivados (ver página 164, líneas 14, 16).

Además parece que la materia de dichas reivindicaciones no esta soportada adecuadamente por la descripción, en particular los ejemplos trabajados en el archivo, desde todos estos ejemplos direccionados solamente a los ácidos alifaticos carboxilicos.

Esta guía automáticamente pregunta, si el problema fundamental de la invención (ver descripción, página 2) puede ser resuelto o declarar efectos técnicos (ver descripción, pagina 49) puede ser llevado a cabo con compuestos de la reivindicación 1 que tiene como residuo R^6 e.g. un ester carboxilico, una amida carboxilica o un grupo tetrazolil.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

WOOD, David, J.
Pfizer Global Research and Developm
Ramsgate Road
Sandwich
Kent CT13 9NJ
GRANDE BRETAGNE

EUROPEAN PHARMA
PATENT DEPARTMENT
30 AUG 2005

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	26.08.2005
Applicant's or agent's file reference PC25631A	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2004/001159	01.04.2004	15.04.2003

Applicant
PFIZER INC. et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	HALBARTSCHLAGER, M Tel. +49 30 25901-714

Form PCT/IPEA/416 (January 2004)

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PC25631A	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/IB2004/001159	International filing date (day/month/year) 01.04.2004	Priority date (day/month/year) 15.04.2003
International Patent Classification (IPC) or national classification and IPC C07D263/00, C07D263/32		
Applicant PFIZER INC. et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the International application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the International application
☐	Box No. VIII	Certain observations on the International application

Date of submission of the demand	Date of completion of this report
30.04.2004	26.08.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized Officer Hoepfner, W Telephone No. +49 30 25901-337

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IB2004/001159

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-162 as originally filed

Claims, Numbers

1-15 as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No. PCT/IB2004/001159

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

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

☐ the entire international application,

☒ claims Nos. 1-13,15 (with respect to inventive step), 14 (with respect to inventive step and industrial applicability)

because:

☒ the said international application, or the said claims Nos. 1-15 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No: PCT/IB2004/001159 348

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2,4-7,10-13
	No:	Claims	1,3,8,9,14,15
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	-
Industrial applicability (IA)	Yes:	Claims	1-13,15
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item III

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

The subject-matter of present claims 1, 3, 8, 9, 14 and 15 is not deemed novel (see paragraph V below). Since it is at present not clear, on which possibly remaining novel subject-matter the present application is to be further based, no opinion will be formulated with respect to inventive step of any possibly remaining novel subject-matter of claims 1-15 (Article 34(4)(a)(ii) PCT).

Apart from the foregoing, the question arises, if such possibly remaining novel subject-matter would meet the requirements of Rule 13 PCT in view of the cited prior art (in particular D1; see paragraph V below), i.e., if such subject-matter could be distinguished from said prior art by means of one single (unitarian) distinguishing feature.

Claim 14 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, the International Examination Authority fully concurs with the objection put forward by the International Search Authority and no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT).

Re Item V

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

D1: WO 02/064130 A (PFIZER PROD INC ; HAYWARD CHERYL MYERS (US); PERRY DAVID AUSTEN (US)) 22 August 2002 (2002-08-22)

D2: EP-A-1 088 824 (PFIZER PROD INC) 4 April 2001 (2001-04-04)

Novelty

The subject-matter of claim 1 overlaps with the subject-matter of D1 the overlapping portions being Q=aryl; Y= -(C=O)-, -SO_2-; Y''= -N(R^{10})-, -O-; R^5= -($CR^{11}R^{12}$)$_m$-; R6= -COOH, -(C=O)-O-(C_1-C_6)alkyl, -(C=O)-N$R^{10}R^{11}$, -(C=O)-NR^{10}-SO_2-R^{11}, tetrazolyl; R^7=R^8=R^{10}=R^{12}=H; R^{11}=H, OH; Ar^3=phenylene; p=2; n=1 (see page 2, lines 19-21; page 2, Formula I; page 16, lines 18-22).

Document D2 discloses further compounds useful in the treatment of diabetes (see page 3, lines 56-58; page 4, Formula I; page 18, lines 14, 18-20).

In view of this prior, it appears that the subject-matter of the present independent claims 1, 14 and 15 and the present dependent claims 3, 8 and 9 lacks novelty.

Industrial applicability

There is no doubt that the subject-matter of the present claims 1-13 and 15 is industrially applicable.

However, for the assessment of the present claim 14 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of a claim. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Formal matters

It appears that the subject-matter of claims 1-6, 8, 10 and 12 is not in line with the title of the invention, since the definition of group R^6 comprises also functional groups other than carboxylic acids or their derivatives (see page 164, lines 14, 16).

It appears furthermore that the subject-matter of the said claims is not adequately supported by the description, in particular the worked Examples on file, since all of these Examples address aliphatic carboxylic acids only.

This leads automatically to the question, if the problem underlying the invention (see description, page 2) can be solved or the alleged technical effect (see description, page 49) can be achieved with compounds of claim 1 having as residue R^6 e.g. a carboxylic ester, a carboxylic amide or a tetrazolyl group.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2004/001159

401

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D263/32 C07C59/125 C07D401/04 C07D411/12 C07D249/06
C07D213/66 C07C61/04 C07D307/79 C07D413/14 C07D417/14
C07D405/06 C07D413/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/064130 A (PFIZER PROD INC ; HAYWARD CHERYL MYERS (US); PERRY DAVID AUSTEN (US)) 22 August 2002 (2002-08-22) page 2, line 19 - line 21 page 2, Formula I page 16, line 18 - line 22	1,3,8,9, 14,15
A	EP 1 088 824 A (PFIZER PROD INC) 4 April 2001 (2001-04-04) page 3, line 56 - line 58 page 4, Formula I page 18, line 14 page 18, line 18 - line 20	1-15

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 September 2004	21/09/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hoepfner, W

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB2004/001159

402

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 02064130 A	22-08-2002	BR 0207227 A	10-02-2004
		CA 2438492 A1	22-08-2002
		EP 1372632 A1	02-01-2004
		WO 02064130 A1	22-08-2002
		JP 2004520397 T	08-07-2004
		US 2002169192 A1	14-11-2002
EP 1088824 A	04-04-2001	AT 257480 T	15-01-2004
		BR 0004582 A	17-04-2001
		CA 2321379 A1	30-03-2001
		DE 60007592 D1	12-02-2004
		DK 1088824 T3	13-04-2004
		EP 1088824 A2	04-04-2001
		EP 1391460 A1	25-02-2004
		ES 2211454 T3	16-07-2004
		JP 3489819 B2	26-01-2004
		JP 2001131181 A	15-05-2001
		PT 1088824 T	30-04-2004
		US 2002183369 A1	05-12-2002
		US 2003195361 A1	16-10-2003
		US 6399601 B1	04-06-2002

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2004/001159

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

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

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

Although claim 14 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

SUPERINDUSTRIA Y COMERCIO
Radicacion : 05102005 [illegible] Folios: 402
Fecha (AMD): 2005-10-07 16:58:40
Tramite : 411 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN ✓ MODELO DE UTILIDAD	( )	( )
- Indicación de que se solicita la concesión de una patente.	( )	(✓)
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	(✓)
- Descripción de la invención.	( )	(✓)
- Dibujos de ser estos pertinentes.	( )	(✓)
- Comprobante de Pago de las tasas establecidas.		
COMPLETA (✓) INCOMPLETA	( )	( )
DISEÑO INDUSTRIAL ( )		
- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta	( )	( )
- la solicitud.		
- Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )
ESQUEMA DE TRAZADO ( )		
- Indicación de que solicita el registro de un Esquema de trazado.	( )	( )
- Datos de identificación del solcitante o de la persona que presenta La solicitud.	( )	( )
Representación gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )

Firma Responsable:

Fecha:

404

REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCI

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REINALDO
Apoderado(a) y/o Representante de
PFIZER INC

REFERENCIA	Radicación No.	5 102555
	Solicitud internacional	IB2004/001159
	Fecha inicio fase nacional	15/11/2005
	Trámite	11
	Evento	379
	Actuación	430
	Oficio No.	13611

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

CLARA DE JAIMES
Jefe de la División de Nuevas Creaciones (E)

El anterior requerimiento fue notificado por fijación en lista de fecha
adpa11 23 DIC. 2005