Industria y Comercio

SUPERINTENDENCIA

PCT

Organizacion CSA Ltda

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISIÓN DE NUEVAS CREACIONES

07-98442

SOLICITUD DE PATENTE DE INVENCIÓN

INVENTARIO

TITULO: DERIVADOS DE PIRROLIDINA 3,4-SUSTITUIDA PARA EL TRATAMIENTO DE HIPERTENSION

IPC 8 A61K 31/4025 // 31/341 // 31/422
A 61 P9/12

SOLICITANTE: NOVARTIS AG

DIRECCIÓN: Lichtstrasse 35, CH-4056 Basel, Suiza

APODERADO: CARLOS A. OLARTE

BOGOTÁ: 21 de Septiembre de 2007

P2007/00144

OlarteRaisbeck

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 07-098442- -00000-0000
Fecha: 2007-09-21 16:44:04 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 963

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2007/000144**

SOLICITUD DE:

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO
23/10/2007

(1) [X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[ ] Capítulo I. [X] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: NOVARTIS AG
Dirección: Lichtstrasse 35, CH-456 Basel
Nacionalidad o Domicilio: Suiza
Lugar de Constitución: Suiza
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 79782747Bta
TP 74.295

INVENTOR (ES) (72)

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

(3) **PCT (86)**

Solicitud Internacional No. PCT/EP2006/002578 Fecha Marzo 21, 2006

Publicación Internacional No. WO 2006/100036 Fecha Septiembre 28, 2006

Título (54) DERIVADOS DE PIRROLIDINA 3,4-SUSTITUIDA PARA EL TRATRAMIENTO DE HIPERTENSION

Clasificación Internacional (51) A61K 31/4025, A61K 31/341, A61K 31/351, A61K 31/357, A61K 31/4035, A61K 31/404, A61K 31/416, A61K 31/422, A61K 31/4409, A61K 31/454, A61K 31/4704, A61K 31/506, A61K 31/5355, A61K 31/5377 A 61 P 9/12

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

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
GB	Marzo 23, 2005	0505969.6

(9) **Comprobante de pago No.** **07-75.605** **Fecha** **18 Septiembre 2007**

(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. Adjunto copia simple ver expediente No. 06-094731
- [x] 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).
- [ ] 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/EP2006/002578

Claus EHRHARDT,
Grossmannstrasse 17,
79541 Lörrach
Alemania
Nacionalidad: Alemana

Osamu IRIE,
Tsukuba Research Institute,
Okubo 8, Tsukuba,
Ibaraki 300-2611
Japón
Nacionalidad: Japonesa

Edwige Liliane Jeanne LORTHIOIS
6, rue des Sapins,
F-68680 Niffer
Francia
Nacionalidad: Francesa

Juergen Klaus MAIBAUM
Luetemannsweg 14/1,
79576 Weil-Haltingen
Alemania
Nacionalidad: Alemana

Nils OSTERMANN
Mühlenstrasse 43,
79589 Binzen
Alemania
Nacionalidad: Alemana

Holger SELLNER
Keltenstrasse 37,
CH-4106 Therwil
Suiza
Nacionalidad: Alemana

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 07-098442- -00000-0000

Fecha: 2007-09-21 16:44:04 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 963

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 75,605
FECHA : SEPTIEMBRE 18 DE 2007

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO POPULAR	050-00110-6	68290537	18/09/2007	7,259,000.00

***** 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	482,000.00
		TOTAL : $	482,000.00

SON: CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Nota del traductor:

El documento adjunto de poder de Novartis AG a Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana Maria Frieri y/o Juan Guillermo Moure y/o Natalia Castro lleva los siguientes datos en inglés.

CERTIFICACIÓN NOTARIAL

1. En esta fecha, día 30 de Agosto de 2006, yo, el suscrito Notario Público certifico por medio del presente la autenticidad de las firmas del señor Arthur Canonica, ciudadano de Corticiasca, Suiza, residente en Wisen/SO, Suiza, y del Sr. Pascal Traub, ciudadano de Riehen, Suiza, residente en Basilea, Suiza, ambos personas mayores de edad y con dirección comercial en Lichstrasse 35, 4056, Basilea, Suiza. La autenticidad de la firmas fue establecida por medio de la comparación.
2. Además, yo, el Notario Público, certifico por el presente que las anteriores personas han ejecutado el anterior documento como apoderados de Novartis AG.
3. Además, yo, el Notario Público certifico por el presente que Novartis AG, con su principal lugar de negocios en Basilea, Suiza, está debidamente constituida, está actualmente vigente y que los propósitos para los cuales se otorgó el Documento de Poder están dentro del alcance de sus propósitos corporativos.

Traductor Oficial
JORGE E. SIERRA REYE
Licencia 376 - 1993 Minis

4. Además, yo, el Notario Público, certifico por el presente que las anteriores personas tienen la autoridad para ejecutar el documento de Poder y que por este instrumento, su representación es legal.

La base para mis certificaciones de los puntos 2, 3 y 4 fue la exhibición de los siguientes documentos auténticos:

- Documento de Poder de Novartis AG fechado el 19 de junio de 2006 y
- Extracto del Registro de Comercio del Cantón de la ciudad de Basilea para Novartis AG, en Basilea, fechado el 25 de enero de 2006.

Basilea, Suiza, este día 30 de Agosto de 2006.

(Firmado) Dr. Matthias Staehelin, Notario Público del Cantón de la ciudad de Basilea, Suiza.

Mi licencia vence el 11 de Marzo de 2009.

Hay una Apostilla de Suiza, firmada por Heidi Fischer, bajo el No. 8049/13584.

Traductor Oficial
JORGE E. SIERRA REYES

Certificación:

Certifico que la presente es una traducción verdadera y completa del documento adjunto: "Novartis"

Fecha: 12 de Septiembre de 2006.

Traductor: Jorge Enrique Sierra Reyes.

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

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

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

E-mail: treseser1@yahoo.com. No. 8346

Traductor Oficial
JORGE E. SIERRA REYE
Licencia 376 - 1993 M...

OLARTE RAISBECK

OLARTE RAISBECK & FRIERI LTDA.

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

Zayde Chahin
Jacqueline Chaparro
José Luis Londoño
Felipe Mendoza
Simón Salinas

Of Counsel
Guillermo Chahin
Graciela Melo

Power of Attorney

Poder

The undersigned,

El suscrito,

NOVARTIS AG

domiciled in

domiciliado en

Lichtstrasse 35, CH-4056 Basel / Switzerland

by means of these presents hereby grants to **Carlos R. Olarte and/or J. Ian Raisbeck and/or Ana María Frieri and/or Juan Guillermo Moure and/or Natalia Castro** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's **Patents for Inventions, Utility Models, Layout-Designs (topographies) of Integrated Circuits, Industrial Designs, Trademarks, Advertising Slogans, Trade Names, Commercial Emblems, Geographical Indications, Protection of Trade Secrets, Obtainer's Certificates, Copyrights, Registration of Domain Names, Health Registrations, or any other intellectual property right** 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, recourses, 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.

por medio del presente otorga a **Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana María Frieri y/o Juan Guillermo Moure y/o Natalia Castro** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de las **Patentes de Invención, Modelos de Utilidad, Esquemas de Trazados de Circuitos Integrados, Diseños Industriales, Marcas, Lemas Comerciales, Nombres Comerciales, Enseñas Comerciales, Denominaciones de Origen, Protección de Secretos Empresariales, Certificados de Obtentor, Derechos de Autor, Registro de Nombres de Dominio, Registros Sanitarios, o cualquier otro bien de propiedad intelectual** 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, recursos, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma:

Arthur Canonica

Pascal Traub

Date/Fecha: June 27, 2006

City,Country/Ciudad,País: Basel, Switzerland

Attestation

1 On this date, the 30th (thirtieth) day of August 2006 (two thousand and six), I, the undersigned Notary Public certify herewith the authenticity of the signatures of **Mr. Arthur Canonica**, citizen of Corticiasca, Switzerland, residing in Wisen/SO, Switzerland and of **Mr. Pascal Traub**, citizen of Riehen, Switzerland, residing in Basel, Switzerland, both of legal age and with business address at, Lichtstrasse 35, 4056 Basel, Switzerland. The authenticity of the signatures was established by means of comparison.

2 Further, I, the Notary Public certify herewith that the foregoing persons have executed the foregoing document as proxy holders for Novartis AG.

3 Further, I, the Notary Public certify herewith that Novartis AG, having its principal place of business located in Basel / Switzerland, 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 Further, I, the Notary Public certify herewith that the foregoing persons have the authority to execute the Power of Attorney and that for this instrument their representation is legal.

The foundation for my certifications contained in points 2 (two), 3 (three) and 4 (four) was the exhibition of the following authentic documents:

- Power of Attorney by Novartis AG dated June 19 (nineteen), 2006 (two thousand and six); and
- Extract from the Register of Commerce of the Canton of Basel-City for Novartis AG, in Basel, dated January 25 (twenty-five), 2006 (two thousand and six).

BASEL, Switzerland, this 30th (thirtieth) day of August 2006 (two thousand and six)

M. Staehelin

Dr. Matthias Staehelin, Notary Public
in the Canton of Basel-City, Switzerland

My license expires on March 11 (eleven), 2009 (two thousand and nine).

Leg.Prot.Nr. 975 /2006

9

APOSTILLE

(Hague Convention of October 5th, 1961)

1. Country: Switzerland (Schweiz / Suisse)
   This official document
2. is signed by ..... Dr. iur. F. Stachelin
3. in his / her function as ..... Staatsschreiber
4. and certified by the seal of the ..... Staatskanzlei

Certified 31. Aug. 2009

5. in Basel (Bâle) 6. on .....
7. by the State Chancery of the Canton of Basel-Stadt .....
8. no. C 0691 - 28'329
9. Seal / stamp: 10. Signature:

Heidi Fischer

STATE CHANCERY * BASLE-CITY *

Traducción oficial de Inglés a Español
Por Gladis Adriana Pérez
Resolución No 0037, de 2002
Otorgada por El Ministerio De Justicia

Caso de Patente: PC/4-34192A

CESIÓN

Por buena y onerosa consideración, del cual se acusa recibo suficiente, nosotros

1. Claus EHRHARDT, Grossmannstrasse 17, 79541 Lorrach, Germany, ciudadano de Alemania.
2. Osamu IRIE, Novartis Pharma K.K., Tsukuba Research Institute, Okubo 8, Tsukuba, Ibaraki 300-2611, Japón, ciudadano de Japón.
3. Edwige Liliane Jeanne LORTHIOIS, 6 rue des sapins, 68680 Niffer, Francia, ciudadano de Francia.
4. Juergen Klaus MAIBAUM, Luetemannsweg 14/1, 79576 Weil-Haltingen, Alemania, cidadano de Alemania.
5. Nils OSTERMANN, Muhlenstrasse 43, 79589 Binzen, Alemania, ciudadano de Alemania.
6. Holger SELLNER, Keitenstrasse 37, 4106 Therwil, Suiza, cidadano de Alemania.

Por medio de la presente vendemos y transferimos a NOVARTIS AG, una compañía constituida bajo las leyes de la confederación Suiza, de Lichstrasse 35, 4056 Basilea, Suiza y sus sucesores, cesionarios y representantes legales todos nuestros derechos titulo e interés para todos los países del mundo, excepto Austria, y **Novartis Pharma GmbH**, una compañía constituida bajo las Leyes de Austria de Bruner Strasse 59, 1230 Vienna, Austria y sus sucesores, cesionarios y representantes legales todos nuestros derechos titulo e interés para Austria (Novartis AG y Novartis Pharma GmbH, llamados de ahora en adelante colectivamente los **CESIONARIOS**) en y para (1) todos nuestros inventos y descubrimientos descritos en la solicitud de patente titulada:

COMPUESTOS ORGÁNICOS

Presentada* en el RO/ el
el _____, 20____, y de acuerdo con la solicitud de Patente Internacional PCT_____, (2) dicha solicitud de patente (3) todas las fases nacionales de dicha solicitud de patente internacional, (4) todas las demás solicitudes de patentes en todas las regiones y países que reivindiquen prioridad de la solicitud de la Gran Bretaña presentada el 23 de marzo de 2005 y de acuerdo con la solicitud numero 0505969.6, (5) todas las continuaciones y divisiones de todas las solicitudes de patentes mencionadas (Incluyendo además continuaciones y divisiones como tal, sin limites de continuaciones de continuaciones de divisiones), ((2)-(5) llamados de ahora en adelante colectivamente "solicitudes de patentes"), (6) todas las patentes que sean concedidas de cualquiera de las solicitudes de patentes mencionadas, (7) todos los registros y confirmaciones y certificados de importación basados en una o mas de las patentes mencionadas y (8) todos los re-otorgamientos, renovaciones, y extensiones de dichas

GLADYS ADRIANA PEREZ J.
TRADUCTOR E INTERPRETE OFICIAL
RESOLUCION NO. 0037 16-01-2002
MINISTERIO DE JUSTICIA

patentes, y certificados de protección adicional basados en dichas patentes (incluyendo el derecho a presentar las solicitudes de patentes de dichos inventos y descubrimientos en nombre de los **CESIONARIOS**, sus designados en cualquier ,o en todos nuestros nombres, a su elección y de acuerdo con las leyes aplicables en todos los países y regiones y todos los derechos de prioridad en todos los países y regiones para todas las solicitudes de patentes mencionadas bajo el convenio internacional para la Protección de la Propiedad Industrial, y todos los demás acuerdos internacionales similares que sean aplicables) así mismo para ser conservada y disfrutada por dichos **CESIONARIOS,** sus sucesores, asignados y representantes legales, proporcionar todos los términos para que todas las patentes puedan ser concedidas, para conservar y disfrutar plenamente y totalmente por nosotros, así mismo como lo harían si esta cesión no hubiera sido vendida y transferida.

GLADYS ADRIANA PEREZ J.
TRADUCTOR E INTERPRETE OFICIAL
RESOLUCION No. 0037 16-01-2002
MINISTERIO DE JUSTICIA

Traducción oficial de Inglés a Español
Por Gladis Adriana Pérez
Resolución No 0037, de 2002
Otorgada por El Ministerio De Justicia

Caso de Patente: PC/4-34192A

*Nosotros por medio del presente autorizamos a los **CESIONARIOS** y sus representantes para incorporar en este instrumento el Número de la solicitud y la fecha de presentación de dicha solicitud cuando esta sea notificada.

Y por medio de la presente nosotros convenimos y acordamos que en cualquier momento, al requerirse y a expensas de los **CESIONARIOS**, ejecutaremos y entregaremos cualquier y todos los documentos necesarios y deseables para perfeccionar el titulo de los anteriores inventos o descubrimientos, solicitudes de patente, patentes, registros confirmaciones, certificados de importación, re-otorgamientos, renovaciones, extensiones certificados de reexaminación, certificados de protección adicional a nombre de los **CESIONARIOS**, sus sucesores, asignados u otros representantes legales, incluyendo la ejecución y consecución de cualquier y todo documento adicional que evidencie esta cesión y venta según sea necesario o deseable para el registro del mismo ante la Oficina de Patentes u otra oficina de propiedad industrial, agencia o de cualquier región o país en cuestión, y que nosotros, en cualquier momento, al requerirse y a expensas de los **CESIONARIOS**, ejecutaremos cualquier solicitud de patente adicional, solicitud para registrar y/o confirmar de una o mas de dichas patentes, solicitudes para certificados de importación basados en una o mas de dichas patentes, solicitudes para re-otorgamientos, renovaciones y extensiones de una o mas de dichas patentes, y certificados de protección adicional basados en una o mas de las patentes mencionadas y realizaremos las declaraciones necesarias juramentadas y realizaremos todos los actos jurídicos necesarios para ello, sin compensación adicional, pero a expensas de los **CESIONARIOS**, sus sucesores, cesionarios, u otros representantes legales.

Ejecutado el 03 de febrero de 2006.
Claus EHRHARDT, (firma ilegible) L.S.

RECONOCIMIENTO

Estado de _____)

Condado de _____)

En este día ___de _____ de 20___, se presentó personalmente ante mi sabiendo, y sabiéndolo yo ser la misma persona descrita en este documento y quien ejecutó el anterior instrumento, y reconoce que el (ella) ejecutó el mismo, por su propia voluntad con los propósitos expuestos.

_____
Notario Público

GLADYS ADRIANA PEREZ J.
TRADUCTORA
RESOLUCION 0037 16-01-2002
MINISTERIO DE JUSTICIA

Ejecutado el 14 de febrero de 2006.
Edwige Liliane Jeanne LORTHIOIS, (firma ilegible) L.S.

RECONOCIMIENTO

Estado de _____)

Condado de _____)

En este día ___de _____ de 20___, se presentó personalmente ante mi sabiendo, y sabiéndolo yo ser la misma persona descrita en este documento y quien ejecutó el anterior instrumento, y reconoce que el (ella) ejecutó el mismo, por su propia voluntad con los propósitos expuestos.

_____
Notario Público

Ejecutado el 03 de febrero de 2006.
Juergen Klaus MAIBAUM, (firma ilegible) L.S.

RECONOCIMIENTO

Estado de _____)

Condado de _____)

En este día ___de _____ de 20___, se presentó personalmente ante mi sabiendo, y sabiéndolo yo ser la misma persona descrita en este documento y quien ejecutó el anterior instrumento, y reconoce que el (ella) ejecutó el mismo, por su propia voluntad con los propósitos expuestos.

_____
Notario Público

GLADYS ADRIANA PEREZ J.
TRADUCTOR INTERPRETE OFICIAL
RESOLUCION No. 0037 16-01-2002
MINISTERIO DE JUSTICIA

Traducción oficial de Inglés a Español
Por Gladis Adriana Pérez
Resolución No 0037, de 2002
Otorgada por El Ministerio De Justicia

Caso de Patente: PC/4-34192A

Ejecutado el 03 de febrero de 2006.
Nils OSTERMANN, (firma ilegible) L.S.

RECONOCIMIENTO

Estado de _____)

Condado de _____)

En este día ___de _____ de 20___, se presentó personalmente ante mi sabiendo, y sabiéndolo yo ser la misma persona descrita en este documento y quien ejecutó el anterior instrumento, y reconoce que el (ella) ejecutó el mismo, por su propia voluntad con los propósitos expuestos.

_____
Notario Público

Ejecutado el 03 de febrero de 2006.
Holger SELLNER, (firma ilegible) L.S.

RECONOCIMIENTO

Estado de _____)

Condado de _____)

En este día ___de _____ de 20___, se presentó personalmente ante mi sabiendo, y sabiéndolo yo ser la misma persona descrita en este documento y quien ejecutó el anterior instrumento, y reconoce que el (ella) ejecutó el mismo, por su propia voluntad con los propósitos expuestos.

_____
Notario Público

GLADYS ADRIANA PEREZ J.
TRADUCTOR T. T. PUBLICO OFICIAL
RESOLUCION No. 0037 16-01-2002
MINISTERIO DE JUSTICIA

51

Traducción oficial de Inglés a Español
Por Gladis Adriana Pérez
Resolución No 0037, de 2002
Otorgada por El Ministerio De Justicia

CESIÓN

Por buena y onerosa consideración, del cual se acusa recibo suficiente, nosotros

7. Claus EHRHARDT, Grossmannstrasse 17 79541 Lorrach, Germany, ciudadano de Alemania.
8. Osamu IRIE, Novartis Pharma K.K., Tsukuba Research Institute, Okubo 8, Tsukuba, Ibaraki 300-2611, Japón, ciudadano de Japón.
9. Edwige Liliane Jeanne LORTHIOIS, 6 rue des sapins, 68680 Niffer, Francia, ciudadano de Francia.
10. Juergen Klaus MAIBAUM, Luetemannsweg 14/1, 79576 Weil-Haltingen, Alemania, cidadano de Alemania.
11. Nils OSTERMANN, Muhlenstrasse 43, 79589 Binzen, Alemania, ciudadano de Alemania.
12. Holger SELLNER, Keitenstrasse 37, 4106 Therwil, Suiza, cidadano de Alemania.

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COMPUESTOS ORGÁNICOS

Presentada* en el RO/ el
el _____, 20____, y de acuerdo con la solicitud de Patente Internacional PCT_____, (2) dicha solicitud de patente (3) todas las fases nacionales de dicha solicitud de patente internacional, (4) todas las demás solicitudes de patentes en todas las regiones y países que reivindiquen prioridad de la solicitud de la Gran Bretaña presentada el 23 de marzo de 2005 y de acuerdo con la solicitud numero 0505969.6, (5) todas las continuaciones y divisiones de todas las solicitudes de patentes mencionadas (Incluyendo además continuaciones y divisiones como tal, sin limites de continuaciones de continuaciones de divisiones), ((2)-(5) llamados de ahora en adelante colectivamente "solicitudes de patentes"), (6) todas las patentes que sean concedidas de cualquiera de las solicitudes de patentes mencionadas, (7) todos los registros y confirmaciones y certificados de importación basados en una o mas de las patentes mencionadas y (8) todos los re-otorgamientos, renovaciones, y extensiones de dichas

GLADYS ADRIANA PEREZ J.
TRADUCTOR INTERPRETE OFICIAL
RESOLUCIÓN No. 0037 16-01-2002
MINISTERIO DE JUSTICIA

patentes, y certificados de protección adicional basados en dichas patentes (incluyendo el derecho a presentar las solicitudes de patentes de dichos inventos y descubrimientos en nombre de los **CESIONARIOS**, sus designados en cualquier ,o en todos nuestros nombres, a su elección y de acuerdo con las leyes aplicables en todos los países y regiones y todos los derechos de prioridad en todos los países y regiones para todas las solicitudes de patentes mencionadas bajo el convenio internacional para la Protección de la Propiedad Industrial, y todos los demás acuerdos internacionales similares que sean aplicables) así mismo para ser conservada y disfrutada por dichos **CESIONARIOS,** sus sucesores, asignados y representantes legales, proporcionar todos los términos para que todas las patentes puedan ser concedidas, para conservar y disfrutar plenamente y totalmente por nosotros, así mismo como lo harían si esta cesión no hubiera sido vendida y transferida.

GLADYS ADRIANA PEREZ J.
TRADUCTOR INTERPRETE OFICIAL
RESOLUCION No. 0037 16-01-2002
MINISTERIO DE JUSTICIA

Traducción oficial de Inglés a Español
Por Gladis Adriana Pérez
Resolución No 0037, de 2002
Otorgada por El Ministerio De Justicia

*Nosotros por medio del presente autorizamos a los **CESIONARIOS** y sus representantes para incorporar en este instrumento el Número de la solicitud y la fecha de presentación de dicha solicitud cuando esta sea notificada.

Y por medio de la presente nosotros convenimos y acordamos que en cualquier momento, al requerirse y a expensas de los **CESIONARIOS**, ejecutaremos y entregaremos cualquier y todos los documentos necesarios y deseables para perfeccionar el titulo de los anteriores inventos o descubrimientos, solicitudes de patente, patentes, registros confirmaciones, certificados de importación, re-otorgamientos, renovaciones, extensiones certificados de reexaminación, certificados de protección adicional a nombre de los **CESIONARIOS**, sus sucesores, asignados u otros representantes legales, incluyendo la ejecución y consecución de cualquier y todo documento adicional que evidencie esta cesión y venta según sea necesario o deseable para el registro del mismo ante la Oficina de Patentes u otra oficina de propiedad industrial, agencia o de cualquier región o país en cuestión, y que nosotros, en cualquier momento, al requerirse y a expensas de los **CESIONARIOS**, ejecutaremos cualquier solicitud de patente adicional, solicitud para registrar y/o confirmar de una o mas de dichas patentes, solicitudes para certificados de importación basados en una o mas de dichas patentes, solicitudes para re-otorgamientos, renovaciones y extensiones de una o mas de dichas patentes, y certificados de protección adicional basados en una o mas de las patentes mencionadas y realizaremos las declaraciones necesarias juramentadas y realizaremos todos los actos jurídicos necesarios para ello, sin compensación adicional, pero a expensas de los **CESIONARIOS**, sus sucesores, cesionarios, u otros representantes legales.

Ejecutado el 09 de febrero de 2006.
Osamu IRIE, (firma ilegible) L.S.

RECONOCIMIENTO

Estado de _____)

Condado de _____)

En este día ___de _____ de 20___, se presentó personalmente ante mi sabiendo, y sabiéndolo yo ser la misma persona descrita en este documento y quien ejecutó el anterior instrumento, y reconoce que el (ella) ejecutó el mismo, por su propia voluntad con los propósitos expuestos.

_____
Notario Público

GLADYS ADRIANA PEREZ J.
TRADUCTOR - INTERPRETE OFICIAL
RESOLUCION No. 0037 16-01-2002
MINISTERIO DE JUSTICIA

Traducción oficial de Inglés a Español
Por Gladis Adriana Pérez
Resolución No 0037, de 2002
Otorgada por El Ministerio De Justicia

Caso de Patente: PC/4-34192A

Sello de Notario
Oficina de Asuntos Legales de Osaka
1-2, HIRANO-MACHI, 2-CHOME,
CHUO-KU, OSAKA JAPON

TESTIFICACION

REGISTRO NÚMERO 135/2006

Por medio de la presente se certifica que Nobuko INAMOTO, un agente de Osamu IRIE, se ha presentado ante mi y ha dicho que Osamu IRIE reconoció el mismo haber firmado el documento adjunto.

De la oficina de Koichiro SHIGEYOSHI, Osaka, Japón el 14 de febrero de 2006.

Firma ilegible

_____
Koichiro SHIGEYOSHI
Notario adjunto a
Oficina de asuntos legales de Osaka

c/o Edificio Sawanotsuru
1-2, Hiranomashi 2-chome
Chuo-ku, Osaka, Japón.

Sello de Notaria:
Oficina de Asuntos Legales de Osaka
1-2, HIRANO-MACHI, 2-CHOME,
CHUO-KU, OSAKA JAPÒN

GLADYS ADRIANA PÉREZ J.
TRADUCTOR E INTERPRETE OFICIAL
RESOLUCION No. 0037 16-01-2002
MINISTERIO DE JUSTICIA

19

ACEPTACIÓN DE LA CESIÓN

Con referencia a la cesión realizada a **NOVARTIS AG** de una invención titulada **"COMPUESTOS ORGANICOS"** firmada por (1) **Claus EHRHARDT**, (2) **Osamu IRIE**, (3) **Edwige lilianE Jeanne LORTHIOIS**, (4) **Juergen Klaus MAIBAUM**, y (5) **Holger SELLNER**; certificamos que dicha cesión ha sido aceptada por **NOVARTIS AG.**

NOVARTIS AG

Por:	(Firma ilegible)	(Firma ilegible)
Nombre:	Ella Rutschmann	Biljana Colovic
Cargo:	Profesionales administrativos	Director de Archivo Extranjero.
Fecha:	27 de febrero de 2006.	

GLADYS ADRIANA PEREZ J.
TRADUCTORE INTERPRETE OFICIAL
RESOLUCION No. 0037 16-01-2002
MINISTERIO DE JUSTICIA

Traducción oficial de Inglés a Español
Por Gladis Adriana Pérez
Resolución No 0037, de 2002
Otorgada por El Ministerio De Justicia

Caso de Patente: PC/4-34192A

TESTIFICACION

Yo, el suscrito notario publico de Basilea, Suiza, certifico por medio del presente la autenticidad de las firmas de arriba son firmas legitimas del Señor Claus Ehrhardt ciudadano Alemán, residente en Lorrach, Alemania, la Señora.Edwige Liliana Jeanne Lorthiois, ciudadana de Francia, residente en Niffer, Francia, el Señor Juergen Klaus Maibaum, ciudadano Alemán, residente en Well-Haltingen, Alemania, el Señor Nils Ostermann, ciudadano Alemán, residente en Binzen, Alemania, y el Señor Holger Seliner, ciudadano Alemán, residente en Therwil, Suiza.

Adicionalmente certifico que las firmas anteriores son las firmas genuinas de la Señora Ella Rutsmann, ciudadana de Lotzwil, Suiza, residente en Basilea, Suiza, y de la Señora Biljana Colovic, ciudadana de Serbia y Montenegro, residente en Basilea, Suiza, Ambas actuando por NOVARTIS AG, en Basilea, Suiza, Ambas como apoderadas con firma compartida.

La autenticidad de las firmas fue demostrada bajo comparación.

BASILEA, Suiza, 01 día del mes de marzo de 2006

(Firma) Dr. M. Staehelin
Notario de Basilea
Leg. Prot. Nr.:294/2006

COPIA FIEL Y VERDADERA

_____
Doctor M. Staehelin
Notario

GLADYS ADRIANA PEREZ J.
TRADUCTOR E INTERPRETE OFICIAL
RESOLUCION No. 0037 16-01-2002
MINISTERIO DE JUSTICIA

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Por Gladis Adriana Pérez
Resolución No 0037, de 2002
Otorgada por El Ministerio De Justicia

Caso de Patente: PC/4-34192A

APOSTILLA

(CONVENCION DE LA HAYA DEL 5 DE OCTUBRE DE 1961)

1. PAIS: SUIZA
2. ESTE DOCUMENTO PÚBLICO HA SIDO FIRMADO POR: Heidi Fisher
3. EN CALIDAD DE: NOTARIO PÚBLICO OFICIAL DE BASILEA, SUIZA
4. CERTIFICADO CON EL SELLO DE: NOTARIO PÚBLICO
   HEIDI FISHER

CERTIFICÓ

5. EN BASILEA, SUIZA
6. EL 21 DE AGOSTO DEL 2007
7. POR: EL ESTADO DE CHANCERY DEL CANTON DE BASILEA-STADT
8. No. 9000/13'983
9. SELLO:
10. FIRMA: HEIDI FISHER

Leg.Prot.Nr.: 1268/2007

Sello de El Estado Chancery, Ciudad de Basilea.

GLADYS ADRIANA PEREZ J.
TRADUCTOR E INTERPRETE OFICIAL
RESOLUCION No. 0037 16-01-2002
MINISTERIO DE JUSTICIA

(joint)

Patent Case PC/4-34192A

~~164~~ 630 CO

ASSIGNMENT

For good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, we

1. **Claus EHRHARDT, Grossmannstrasse 17, 79541 Lörrach, Germany, citizen of Germany**
2. **Osamu IRIE, Novartis Pharma K.K., Tsukuba Research Institute, Okubo 8, Tsukuba, Ibaraki 300-2611, Japan, citizen of Japan**
3. **Edwige Liliane Jeanne LORTHIOIS, 6, rue des sapins, 68680 Niffer, France, citizen of France**
4. **Juergen Klaus MAIBAUM, Luetemannsweg 14/1, 79576 Weil-Haltingen, Germany, citizen of Germany**
5. **Nils OSTERMANN, Mühlenstrasse 43, 79589 Binzen, Germany, citizen of Germany**
6. **Holger SELLNER, Keltenstrasse 37, 4106 Therwil, Switzerland, citizen of Germany**

do hereby sell, assign and transfer to Novartis AG, a company organized under the laws of the Swiss Confederation, of Lichtstrasse 35, 4056 Basel, Switzerland, and its successors, assigns and legal representatives, all our right, title and interest for all countries of the world except Austria and to Novartis Pharma GmbH, a company organized under the laws of Austria, of Brunner Strasse 59, 1230 Vienna, Austria, and its successors, assigns and legal representatives, all our right, title and interest for Austria (Novartis AG and Novartis Pharma GmbH hereinafter referred to collectively as the "**ASSIGNEES**") in and to (1) all of our inventions and discoveries described in the patent application(s) entitled

ORGANIC COMPOUNDS

filed* in the RO/ on

on _____, 20____, and accorded International Patent Application Number PCT _____, (2) said patent application(s), (3) (3) all national stages of said international patent application, (4) all other patent applications in all countries and regions claiming the priority of the Great Britain patent application filed on March 23, 2005 and accorded Application Number 0505969.6, (5) all continuations and divisions of all of said patent applications (including further continuations and divisions such as, but not limited to, continuations of continuations and continuations of divisions), ((2)-(5) hereinafter referred to collectively as "patent applications"), (6) all patents that are granted on any of said patent applications, (7) all registrations and confirmations of, and importation certificates based on, one or more of said patents and (8) all reissues, renewals and extensions of said patents, reexamination certificates issued for said patents and supplementary protection certificates based on said patents (including the right to file patent applications on said inventions and discoveries in the names of **ASSIGNEES**, their designees or in any or all of our names, at their election and in accordance with applicable law in all countries and regions and all rights of priority in all countries and regions for all of said patent applications under the International Convention for the Protection of Industrial Property, and all other applicable similar international agreements), the same to be held and enjoyed by said **ASSIGNEES**, their successors, assigns and legal representatives, to the full ends of the terms for which all patents therefor may be granted, as fully and entirely as the same would have been held and enjoyed by us if this sale, assignment and transfer had not been made.

2 3

(joint) **Patent Case PC/4-34192A**

*We hereby authorize **ASSIGNEES** and their representatives to insert in this instrument the Application Number and the filing date of said patent application when notified thereof.

And we hereby covenant and agree that we will, at any time, upon the request and at the expense of **ASSIGNEES**, execute and deliver all documents that may be necessary or desirable to perfect the title to the foregoing inventions and discoveries, patent applications, patents, registrations, confirmations, importation certificates, reissues, renewals, extensions, reexamination certificates and supplementary protection certificates in **ASSIGNEES**, their successors, assigns or other legal representatives, including the execution and procurement of all further documents evidencing this sale, assignment and transfer as may be necessary or desirable for recording the same in the patent office or other intellectual property office, agency or the like of any country or region, that we will, at any time, upon the request and at the expense of **ASSIGNEES**, execute all additional patent applications, applications for registration and/or confirmation of one or more of said patents, applications for certificates of importation based on one or more of said patents, applications for reissues, renewals and extensions of one or more of said patents and supplemental protection certificates based upon one or more of said patents, and that we will make all rightful oaths and declarations and do all lawful acts requisite for procuring the same or for aiding therein, without further compensation, but at the expense of **ASSIGNEES**, the successors, assigns or other legal representatives.

Executed this 03 day of FEB, 2006

Claus Ehrhardt L.S.

Claus EHRHARDT

ACKNOWLEDGEMENT

State of _____)

) s.s.:

County of _____)

On this _____ day of _____, 20____, personally appeared before me _____ to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____

Notary Public

(joint)

Patent Case PC/4-34192A

Executed this _____ day of _____, 20__.

_____ L.S.
Osamu IRIE

ACKNOWLEDGEMENT

State of _____)
) s.s.:
County of _____)

On this _____ day of _____, 20__, personally appeared before me to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this 14 day of Feb, 2006.

Edwige Lorthiois L.S.
Edwige Liliane Jeanne LORTHIOIS

ACKNOWLEDGEMENT

State of _____)
) s.s.:
County of _____)

On this _____ day of _____, 20__, personally appeared before me to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

(joint) **Patent Case PC/4-34192A**

Executed this 03 day of Feb, 2006

Jürgen Maibaum L.S.

Juergen Klaus MAIBAUM

ACKNOWLEDGEMENT

State of _____)
) s.s.:
County of _____)

On this _____ day of _____, 20__, personally appeared before me to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this 03 day of Feb, 2006.

_____ L.S.

Nils OSTERMANN

ACKNOWLEDGEMENT

State of _____)
) s.s.:
County of _____)

On this _____ day of _____, 20__, personally appeared before me to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

(joint)

Patent Case PC/4-34192A

Executed this 03 day of Feb., 2006

Holger Sellner L.S.

Holger SELLNER

ACKNOWLEDGEMENT

State of _____)
) s.s.:
County of _____)

On this _____ day of _____, 20__, personally appeared before me to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

2

(joint)

Patent Case PC/4-34192A

ASSIGNMENT

For good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, we

1. **Claus EHRHARDT, Grossmannstrasse 17, 79541 Lörrach, Germany, citizen of Germany**
2. **Osamu IRIE, Novartis Pharma K.K., Tsukuba Research Institute, Okubo 8, Tsukuba, Ibaraki 300-2611, Japan, citizen of Japan**
3. **Edwige Liliane Jeanne LORTHIOIS, 6, rue des sapins, 68680 Niffer, France, citizen of France**
4. **Juergen Klaus MAIBAUM, Luetemannsweg 14/1, 79576 Weil-Haltingen, Germany, citizen of Germany**
5. **Nils OSTERMANN, Mühlenstrasse 43, 79589 Binzen, Germany, citizen of Germany**
6. **Holger SELLNER, Keltenstrasse 37, 4106 Therwil, Switzerland, citizen of Germany**

do hereby sell, assign and transfer to Novartis AG, a company organized under the laws of the Swiss Confederation, of Lichtstrasse 35, 4056 Basel, Switzerland, and its successors, assigns and legal representatives, all our right, title and interest for all countries of the world except Austria and to Novartis Pharma GmbH, a company organized under the laws of Austria, of Brunner Strasse 59, 1230 Vienna, Austria, and its successors, assigns and legal representatives, all our right, title and interest for Austria (Novartis AG and Novartis Pharma GmbH hereinafter referred to collectively as the "**ASSIGNEES**") in and to (1) all of our inventions and discoveries described in the patent application(s) entitled

ORGANIC COMPOUNDS

filed* in the RO/ on

on _____, 20____, and accorded International Patent Application Number PCT _____, (2) said patent application(s), (3) (3) all national stages of said international patent application, (4) all other patent applications in all countries and regions claiming the priority of the Great Britain patent application filed on March 23, 2005 and accorded Application Number 0505969.6, (5) all continuations and divisions of all of said patent applications (including further continuations and divisions such as, but not limited to, continuations of continuations and continuations of divisions), ((2)-(5) hereinafter referred to collectively as "patent applications"), (6) all patents that are granted on any of said patent applications, (7) all registrations and confirmations of, and importation certificates based on, one or more of said patents and (8) all reissues, renewals and extensions of said patents, reexamination certificates issued for said patents and supplementary protection certificates based on said patents (including the right to file patent applications on said inventions and discoveries in the names of **ASSIGNEES**, their designees or in any or all of our names, at their election and in accordance with applicable law in all countries and regions and all rights of priority in all countries and regions for all of said patent applications under the International Convention for the Protection of Industrial Property, and all other applicable similar international agreements), the same to be held and enjoyed by said **ASSIGNEES**, their successors, assigns and legal representatives, to the full ends of the terms for which all patents therefor may be granted, as fully and entirely as the same would have been held and enjoyed by us if this sale, assignment and transfer had not been made.

(joint)

Patent Case PC/4-34192A

*We hereby authorize **ASSIGNEES** and their representatives to insert in this instrument the Application Number and the filing date of said patent application when notified thereof.

And we hereby covenant and agree that we will, at any time, upon the request and at the expense of **ASSIGNEES**, execute and deliver all documents that may be necessary or desirable to perfect the title to the foregoing inventions and discoveries, patent applications, patents, registrations, confirmations, importation certificates, reissues, renewals, extensions, reexamination certificates and supplementary protection certificates in **ASSIGNEES**, their successors, assigns or other legal representatives, including the execution and procurement of all further documents evidencing this sale, assignment and transfer as may be necessary or desirable for recording the same in the patent office or other intellectual property office, agency or the like of any country or region, that we will, at any time, upon the request and at the expense of **ASSIGNEES**, execute all additional patent applications, applications for registration and/or confirmation of one or more of said patents, applications for certificates of importation based on one or more of said patents, applications for reissues, renewals and extensions of one or more of said patents and supplemental protection certificates based upon one or more of said patents, and that we will make all rightful oaths and declarations and do all lawful acts requisite for procuring the same or for aiding therein, without further compensation, but at the expense of **ASSIGNEES**, the successors, assigns or other legal representatives.

Executed this _____ day of _____, 20__.

_____ L.S.
Claus EHRHARDT

ACKNOWLEDGEMENT

State of _____)
) s.s.:
County of _____)

On this _____ day of _____, 20____, personally appeared before me _____ to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

(joint) **Patent Case PC/4-34192A**

Executed this 9th day of Feb., 2006.

_____ L.S.
Osamu IRIE

OSAKA LEGAL AFFAIRS BUREAU
"NOTARY"
1-2, HIRANO-MACHI, 2-CHOME,
CHUO-KU, OSAKA JAPAN

ACKNOWLEDGEMENT

State of _____)
) s.s.:
County of _____)

On this _____ day of _____, 20__, personally appeared before me to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this _____ day of _____, 20__.

_____ L.S.
Edwige Liliane Jeanne LORTHIOIS

ACKNOWLEDGEMENT

State of _____)
) s.s.:
County of _____)

On this _____ day of _____, 20__, personally appeared before me to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

(joint) **Patent Case PC/4-34192A**

Executed this _____ day of _____, 20__.

_____ L.S.
Juergen Klaus MAIBAUM

ACKNOWLEDGEMENT

State of _____)
) s.s.:
County of _____)

On this _____ day of _____, 20__, personally appeared before me to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this _____ day of _____, 20__.

_____ L.S.
Nils OSTERMANN

ACKNOWLEDGEMENT

State of _____)
) s.s.:
County of _____)

On this _____ day of _____, 20__, personally appeared before me to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this _____ day of _____, 20__.

_____ L.S.
Holger SELLNER

ACKNOWLEDGEMENT

State of _____)
) s.s.:
County of _____)

On this _____ day of _____, 20__, personally appeared before me to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

登簿平成１８年第 135 号

嘱託人　入　江　　統は、代理人稲本暢子を通じ当公証人の面前で、別紙編綴の証書にある上記嘱託人の署名は同嘱託人がしたものであることを自認する旨陳述した。――――――

よってこれを認証する。――――――

平成１８年２月１４日 ――――――

公証人重吉孝一郎役場において。――――――

大阪市中央区平野町２丁目１番２号（沢の鶴ビル内）

大阪法務局所属

公証人　重吉孝一郎

大阪法務局所属 公証人役場

NOTARIAL ATTESTATION

REGISTER NUMBER: 135 /2006

This is to certify that Nobuko INAMOTO, an agent of Osamu IRIE, has stated in my very presence that said Osamu IRIE acknowledged himself to have signed the attached document.

At the Office of Koichiro SHIGEYOSHI, Osaka, Japan
on the 14th day of February, 2006

Koichiro Shigeyoshi
Koichiro SHIGEYOSHI
Notary attached to
The Osaka Legal Affairs Bureau

c/o Sawanotsuru Building
1-2, Hiranomachi 2-chome
Chuo-ku, Osaka, Japan

OSAKA LEGAL AFFAIRS BUREAU
"NOTARY"
1-2, HIRANO-MACHI, 2-CHOME,
CHUO-KU, OSAKA JAPAN

Case PC/4-34192A

ACCEPTANCE OF ASSIGNMENT

With reference to the Assignment to **NOVARTIS AG** of an invention entitled "**ORGANIC COMPOUNDS**" signed by **Claus EHRHARDT, Osamu IRIE, Edwige Liliane Jeanne LORTHIOIS, Juergen Klaus MAIBAUM, Nils OSTERMANN and Holger SELLNER**; this will certify that **NOVARTIS AG** accepts such Assignment.

NOVARTIS AG

By E. Rutschmann B. Colovic

Name	Ella Rutschmann	Biljana Colovic
Function	Administrative Professional	Head of Foreign Filing

Date: 27.02.2006

35

Attestation

the undersigned notary public of Basel, Switzerland, certify herewith the authenticity of the signatures of **Mr. Claus Ehrhardt**, German citizen, residing in Lörrach, Germany, **Mrs. Edwige Liliane Jeanne Lorthiois**, French citizen, residing in Niffer, France, **Mr. Juergen Klaus Maibaum**, German citizen, residing in Weil-Haltingen, Germany, **Mr. Nils Ostermann**, German citizen, residing in Binzen, Germany, and **Mr. Holger Sellner**, German citizen, residing in Therwil, Switzerland.

Further I certify that the above signatures are the genuine signatures of **Mrs. Ella Rutschmann**, citizen of Lotzwil, Switzerland, residing in Basel, Switzerland, and **Mrs. Biljana Colovic**, citizen of Serbia & Montenegro, residing in Basel, Switzerland, both acting for **Novartis AG**, in Basel, Switzerland, both as proxy holders, both with joint signature.

The authenticity of the signatures was established by comparison.

BASEL, this 1st (first) day of March 2006 (twothousandandsix).

M. Staehelin, Note

Dr. M. Staehelin
Notar

Leg.Prot.Nr.: 294 /2006

For true photocopy

BASEL, Switzerland, this 20th (twentieth) day of August 2007 (two thousand and seven).

M. Staehelin, Notar

Dr. M. Staehelin
Notar

Leg.Prot.Nr. 1268/2007

APOSTILLE

(Hague Convention of October 5th, 1961)

1. Country: Switzerland (Schweiz / Suisse)
   This official document
2. is signed by ..... M. Staehelin .....
3. in his/her function as ..... Gf. Notar .....
4. and certified by the seal of the ..... Grundbuch .....

Certified 21. Aug. 2007

5. in Basel (Bâle) 6. on .....
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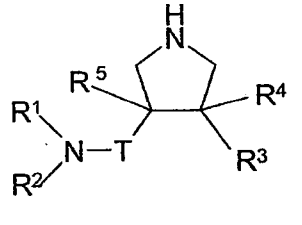
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(I)

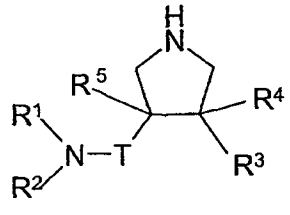
(57) Abstract: The invention relates to the use of (3,4-di-, 3,3,4-tri, 3,4,4-tri- or 3,3,4,4-tetra-)substituted pyrrolidine compounds for the preparation of a pharmaceutical formulation for the treatment of a disease that depends on activity of renin; the use of a compound of that class in the treatment of a disease that depends on activity of renin; compounds that are part of a subclass of these substituted pyrrolidine compounds for use in the diagnostic and therapeutic treatment of a warm-blooded animal, especially for the treatment of a disease (= disorder) that depends on activity of renin; new compounds that are part of a subclass of these substituted pyrrolidine compounds; pharmaceutical formulations comprising said substituted pyrrolidine compounds, and/or a method of treatment comprising administering said substituted pyrrolidine compounds, a method for the manufacture especially of said new substituted pyrrolidine compounds, as well as novel intermediates, starting materials and/or partial steps for their synthesis. The substituted pyrrolidine compounds are of the formula (I), wherein R^1, R^2, R^3, R^4, R^5 and T are defined as in the specification.

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3,4-SUBSTITUTED PYRROLIDINE DERIVATIVES FOR THE TREATMENT OF HYPERTENSION

The invention relates to the use of (3,4-di-, 3,3,4,- tri, 3,4,4-tri- or 3,3,4,4-tetra-)substituted pyrrolidine compounds for the preparation of a pharmaceutical formulation for the treatment of a disease that depends on activity of renin; the use of a compound of that class in the treatment of a disease that depends on activity of renin; compounds that are part of a subclass of these substituted pyrrolidine compounds for use in the diagnostic and therapeutic treatment of a warm-blooded animal, especially for the treatment of a disease (= disorder) that depends on activity of renin; new compounds that are part of a subclass of these substituted pyrrolidine compounds; pharmaceutical formulations or products comprising said substituted pyrrolidine compounds, and/or a method of treatment comprising administering said substituted pyrrolidine compounds, a method for the manufacture especially of said new substituted pyrrolidine compounds, as well as novel intermediates, starting materials and/or partial steps for their synthesis.

Especially, the invention relates to the use of a compound of the formula I,



(I)

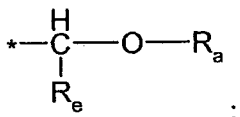
as described in the claims or wherein

R^1 is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, unsubstituted or substituted alkenyl, substituted or unsubstituted alkynyl or acyl;

R^2 is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, unsubstituted or substituted alkenyl, substituted or unsubstituted alkynyl or acyl;

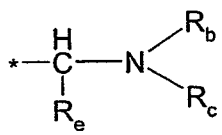
R^3 is a moiety selected from the group of moieties of the formulae

(a)

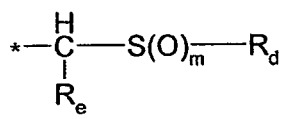


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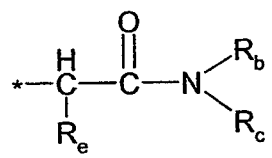
(b)



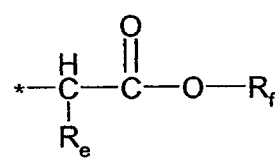
(c)



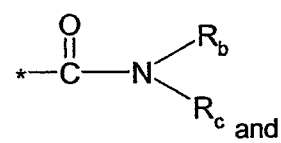
(d)



(e)

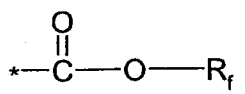


(f)



and

(g)



,

where in any of the moieties of the formulae given above under (a), (b), (c), (d), (e), (f) and (g) the asterisk (*) shows the bond binding the respective moiety R^3 to the rest of the molecule in formula I,

R_a is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, acyl or hydrogen;
R_b and R_c are independently selected from the moieties given under R_a, with the proviso that preferably not more than one of R_b and R_c is acyl,
Rd is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or (preferably if m is 0) acyl, or can have one of these meanings or can be $-N(R_b)(R_c)$ if m is 1 or preferably 2;
R_e is hydrogen, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or (especially) substituted or preferably unsubstituted C_1-C_7-alkyl; and
R_f is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl;
m is 0, 1 or 2;
each of R^4 and R^5 is selected, independently from the other, from hydrogen, unsubstituted or substituted alkyl, hydroxy or esterified or etherified hydroxy;
and T is methylene ($-CH_2-$), methylene mono-substituted by alkyl (-[C(H)(alkyl)]-) , carbonyl (-C(=O)-) or thiocarbonyl (-C(=S)-);
or a pharmaceutically acceptable salt thereof,
in the preparation of a pharmaceutical formulation for the treatment of a disease that depends on activity of renin, especially hypertension.

The compounds of the present invention exhibit inhibitory activity on the natural enzyme renin. Thus, compounds of formula I may be employed for the treatment (this term also including prophylaxis) of one or more disorders or diseases selected from, *inter alia*, hypertension, atherosclerosis, unstable coronary syndrome, congestive heart failure, cardiac hypertrophy, cardiac fibrosis, cardiomyopathy postinfarction, unstable coronary syndrome,

diastolic dysfunction, chronic kidney disease, hepatic fibrosis, complications resulting from diabetes, such as nephropathy, vasculopathy and neuropathy, diseases of the coronary vessels, restenosis following angioplasty, raised intra-ocular pressure, glaucoma, abnormal vascular growth, hyperaldosteronism, cognitive impairment, alzheimers, dementia, anxiety states and cognitive disorders, especially as far as these diseases can be modulated (more especially beneficially influenced) by renin inhibition.

Listed in the claims and below are definitions of various terms used to describe the compounds of the present invention as well as their use and synthesis, starting materials and intermediates and the like. These definitions, either by replacing one, more than one or all general expressions or symbols used in the present disclosure and thus yielding preferred embodiments of the invention, preferably apply to the terms as they are used throughout the specification unless they are otherwise limited in specific instances either individually or as part of a larger group.

The term "lower" or "C_1-C_7-" defines a moiety with up to and including maximally 7, especially up to and including maximally 4, carbon atoms, said moiety being branched (one or more times) or straight-chained and bound via a terminal or a non-terminal carbon. Lower or C_1-C_7-alkyl, for example, is n-pentyl, n-hexyl or n-heptyl or preferably C_1-C_4-alkyl, especially as methyl, ethyl, n-propyl, sec-propyl, n-butyl, isobutyl, sec-butyl, tert-butyl.

Halo or halogen is preferably fluoro, chloro, bromo or iodo, most preferably fluoro, chloro or bromo. If not explicitly or implicitly stated otherwise, halo can also stand for more than one halogen substituent in moieties such as alkyl, alkanoyl and the like (e.g. in trifluoromethyl, trifluoroacetyl).

Unsubstituted or substituted mono- or bicyclic aryl preferably is a mono- or bicyclic aryl with 6 to 22 carbon atoms, especially phenyl, indenyl or naphthyl, and is unsubstituted or substituted by one or more, especially one to three, moieties, preferably independently selected from the group consisting of

a substituent of the formula -(C_0-C_7-alkylene)-$(X)_r$-(C_1-C_7-alkylene)-$(Y)_s$-(C_0-C_7-alkylene)-H (especially in substituted aryl or substituted aryl-alkyl as R^1) where C_0-alkylene means that a bond is present instead of bound alkylene, alkylene in each case may be straight-chained or branched and unsubstituted or (with lower preference) substituted e.g. by one or more

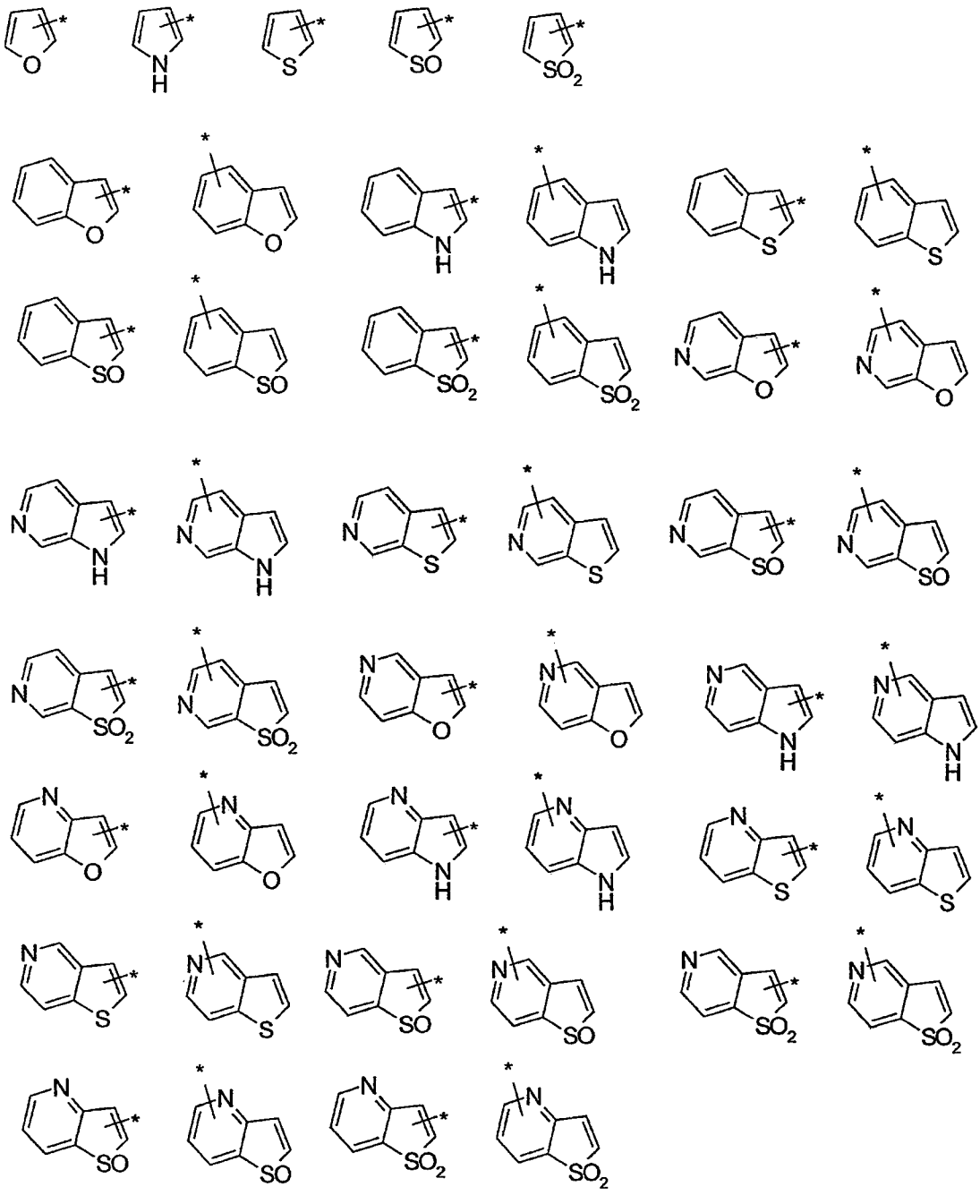
moieties as defined for substituted alkyl, especially by halo, especially fluoro, hydroxy, C_1-C_7-alkoxy, phenyloxy, naphthyloxy, C_1-C_7-alkanoyloxy, benzoyloxy, naphthoyloxy, amino, mono- or di-(C_1-C_7-alkyl, C_1-C_7-alkanoyl, phenyl-C_1-C_7-alkanoyl, naphthyl-C_1-C_7-alkanoyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-amino, carboxy, C_1-C_7-alkoxycarbonyl or cyano, r and s, each independently of the other, are 0 or 1 and each of X and Y, if present and independently of the others, is -O-, -NV-, -S-, -O-CO-, -CO-O-, -NV-CO-; -CO-NV-; -NV-SO_2-, -SO_2-NV; -NV-CO-NV-, -NV-CO-O-, -O-CO-NV-, -NV-SO_2-NV- wherein V is hydrogen or unsubstituted or substituted alkyl as defined below, especially C_1-C_7-alkyl, or is phenyl, naphthyl, phenyl- or naphthyl-C_1-C_7-alkyl or halo-C_1-C_7-alkyl; e.g. C_1-C_7-alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl or tert-butyl, halo-C_1-C_7-alkyl, such as trifluoromethyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, such as 3-methoxypropyl or 2-methoxyethyl, C_1-C_7-alkoxy-C_1-C_7-alkoxy-C_1-C_7-alkyl, phenyloxy- or naphthyloxy-C_1-C_7-alkyl, C_1-C_7-alkanoyloxy-C_1-C_7-alkyl, amino-C_1-C_7-alkyl, such as aminomethyl, C_1-C_7-alkoxy-C_1-C_7-alkylamino-C_1-C_7-alkyl, mono- or di- (C_1-C_7-alkyl-, naphthyl-, phenyl, naphthyl-C_1-C_7-alkyl and/or phenyl-C_1-C_7-alkyl)-amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino-C_1-C_7-alkyl, C_1-C_7-alkyl-O-CO-NH-C_1-C_7-alkyl, C_1-C_7-alkylsulfonylamino-C_1-C_7-alkyl, C_1-C_7-alkyl-NH-CO-NH-C_1-C_7-alkyl, C_1-C_7-alkyl-NH-SO_2-NH-C_1-C_7-alkyl, C_1-C_7-alkoxy, hydroxy-C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7alkoxy, C_1-C_7-alkanoyloxy, halo-C_1-C_7-alkoxy, such as trifluoromethoxy, phenyl- or naphthyl-C_1-C_7-alkanoyloxy, phenyl- or naphthyl-C_1-C_7-alkylaminocarbonyloxy, halo-C_1-C_7-alkylthio, such as trifluoromethylthio, phenyl- or naphthyl-C_1-C_7-alkylthio, mono- or di-(C_1-C_7-alkyl-, naphthyl-C_1-C_7-alkyl-, phenyl-C_1-C_7-alkyl- and/or C_1-C_7-alkoxy-C_1-C_7-alkyl-)amino, C_1-C_7-alkanoylamino, C_1-C_7-alkylsulfonylamino, phenyl- or naphthyl-C_1-C_7-alkanoylamino, phenyl- or naphthyl-C_1-C_7-alkylaminocarbonylamino, carboxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-carbonyl, hydroxy-C_1-C_7-alkoxycarbonyl, C_1-C_7-alkoxy-C_1-C_7-alkoxycarbonyl, amino-C_1-C_7-alkoxycarbonyl, (N-) mono-(C_1-C_7-alkyl)-amino-C_1-C_7-alkoxycarbonyl, C_1-C_7-alkanoylamino-C_1-C_7-alkoxycarbonyl, N-mono- or N,N-di-(C_1-C_7-alkyl, naphthyl-C_1-C_7.alkyl and/ or phenyl-C_1-C_7-alkyl)-aminocarbonyl, C_1-C_7-alkylsulfonyl, halo-C_1-C_7-alkylsulfonyl, hydroxy-C_1-C_7-alkylsulfonyl, C_1-C_7-alkoxy-C_1-C_7-alkylsulfonyl, amino-C_1-C_7-alkylsulfonyl, N-mono- or di-(C_1-C_7-alkyl)-amino-C_1-C_7-alkylsulfonyl, C_1-C_7-alkanoylamino-C_1-C_7-alkylsulfonyl, N-C_1-C_7-alkoxy-C_1-C_7-alkylcarbamoyl or N-mono- or N,N-di-(C_1-C_7-alkyl)-aminosulfonyl;

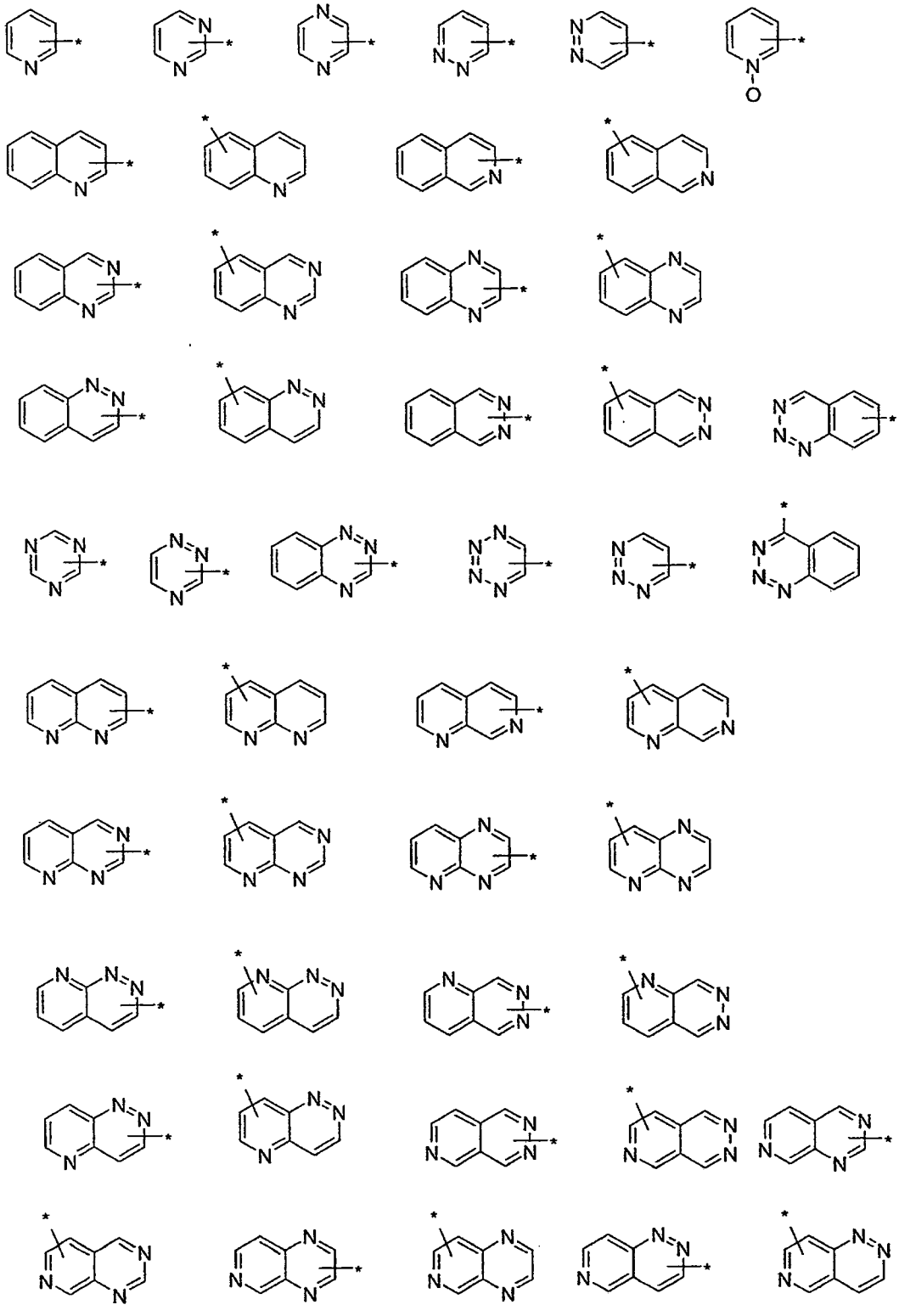
from C_2-C_7-alkenyl, C_2-C_7-alkynyl, phenyl, naphtyl, mono- or bicyclic heterocyclyl, especially as defined below for mono- or bicyclic heterocyclyl, preferably selected from pyrrolyl, furanyl,

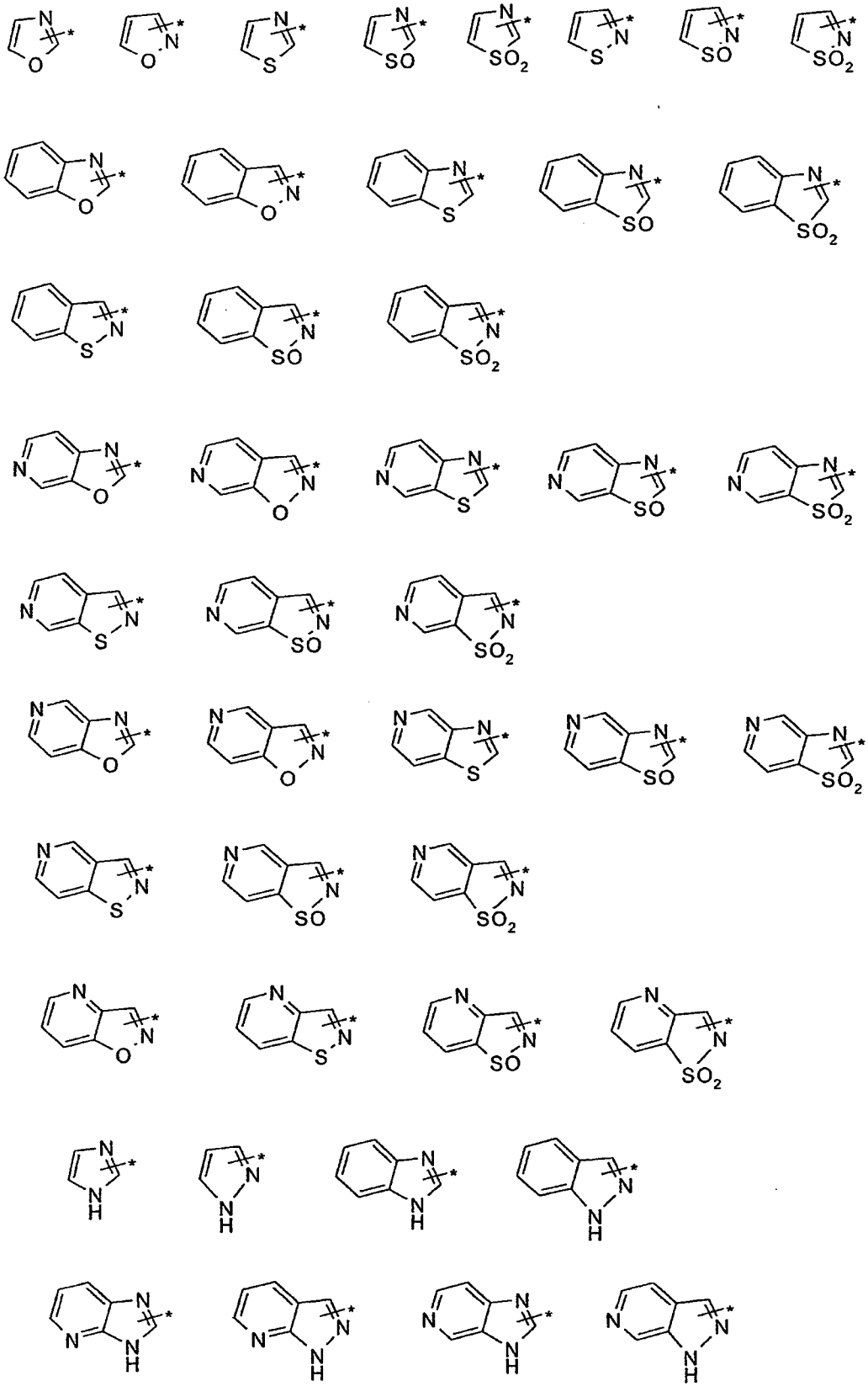
thienyl, pyrimidine-2,4-dione-1-, -3- or –5-yl and tetrahydrofuranyl, , phenyl- or naphthyl- or (mono- or bicyclic heterocyclyl)-C_1-C_7-alkyl or C_1-C_7-alkyloxy wherein mono- or bicyclic heterocyclyl is as defined below, preferably selected from pyrrolyl, furanyl, tetrahydrofuranyl, tetrahydropyranyl and thienyl ; such as benzyl or naphthylmethyl, tetrahydrofuranyl- or tetrahydropyranyl-C_1-C_7-alkyloxycarbonyl, benzoyl- or naphthoylamino-C_1-C_7-alkyl, (phenyl- or naphthyl- or mono- or bicyclic heterocyclyl)-sulfonylamino-C_1-C_7-alkyl wherein phenyl or naphthyl or mono- or bicyclic heterocyclyl is unsubstituted or substituted, preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkylsulfonylamino-C_1-C_7-alkyl, halo, hydroxy, phenyl-C_1-C_7-alkoxy wherein phenyl is preferably unsubstituted or substituted, preferably by C_1-C_7-alkoxy and/or halo, mono- or bicyclic heterocyclyl-C_1-C_7-alkoxy, (mono- or bicyclic heterocyclyl or phenyl or naphthyl)-oxy, naphthyl-C_1-C_7-alkyloxy, benzoyl or naphthoyl or mono- or bicyclic heterocyclylcarbonyl)-oxy, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-aminocarbonyloxy, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-thio, (benzoyl or naphthoyl or mono- or bicyclic heterocyclyl)-thio, nitro, amino, di-((naphthyl or phenyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkyl)-amino, (benzoyl or naphthoyl or mono- or bicyclic heterocyclyl)-amino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-sulfonylamino wherein phenyl or naphthyl is unsubstituted or substituted preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkylsulfonylamino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-aminocarbonylamino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-oxycarbonylamino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkyloxycarbonylamino, carboxyl, C_1-C_7-alkyl-carbonyl, halo-C_1-C_7-alkylcarbonyl, hydroxy-C_1-C_7-alkylcarbonyl, C_1-C_7-alkoxy-C_1-C_7-alkylcarbonyl, amino-C_1-C_7-alkylcarbonyl, (N-) mono- or (N,N-) di-(C_1-C_7-alkyl)-amino-C_1-C_7-alkylcarbonyl, C_1-C_7-alkanoylamino-C_1-C_7-alkylcarbonyl, halo-C_1-C_7-alkoxycarbonyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-oxy-carbonyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkoxycarbonyl, (N,N-) di-(C_1-C_7-alkyl)-amino-C_1-C_7-alkoxycarbonyl, carbamoyl, N-mono or N,N-di-(naphthyl or phenyl or mono- or bicyclic heterocyclyl)-aminocarbonyl, cyano, C_1-C_7-alkylene which is unsubstituted or substituted by up to four C_1-C_7-alkyl substituents and bound to two adjacent ring atoms of the aryl moiety, sulfenyl, sulfinyl, C_1-C_7-alkylsulfinyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-sulfinyl wherein phenyl or naphthyl is unsubstituted or substituted preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, phenyl- or naphthyl-C_1-C_7-alkylsulfinyl, sulfonyl, (phenyl or naphthyl or mono- or bicyclic

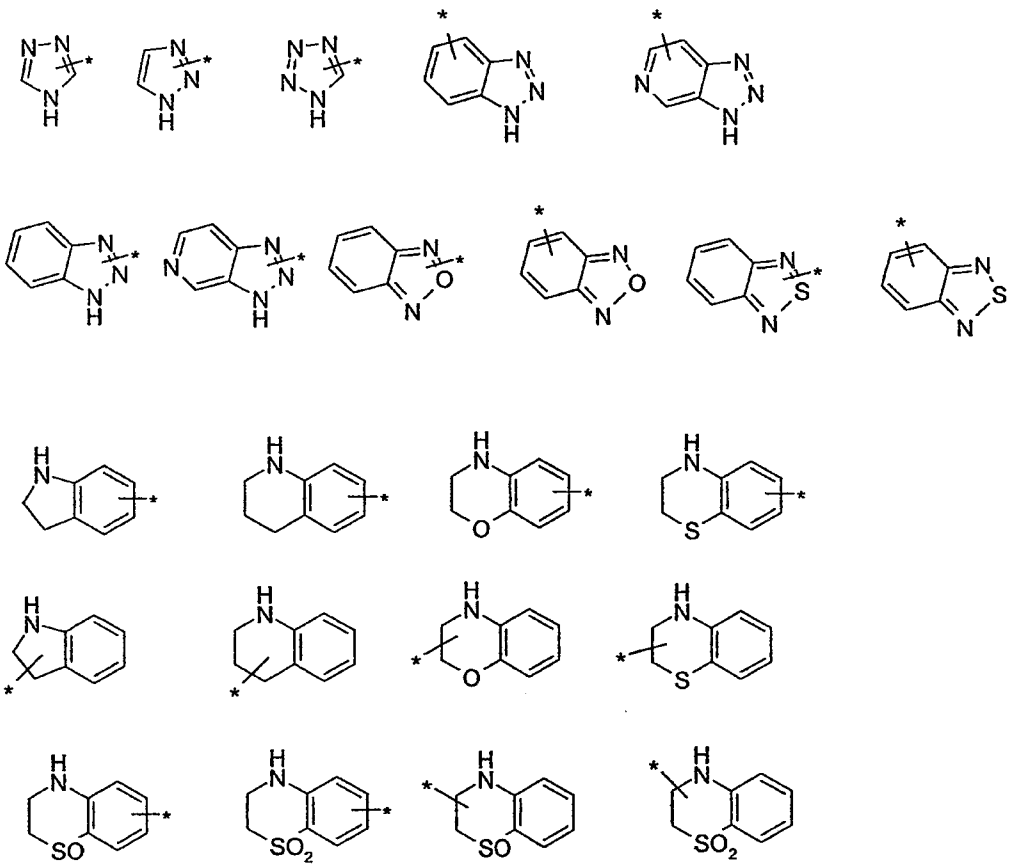
heterocyclyl)-sulfonyl wherein phenyl or naphthyl is unsubstituted or substituted preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkylsulfonyl, sulfamoyl and N-mono or N,N-di-(C_1-C_7-alkyl, phenyl-, naphthyl, mono- or bicyclic heterocyclyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl and/or mono- or bicyclic heterocyclyl-C_1-C_7-alkyl)-aminosulfonyl;

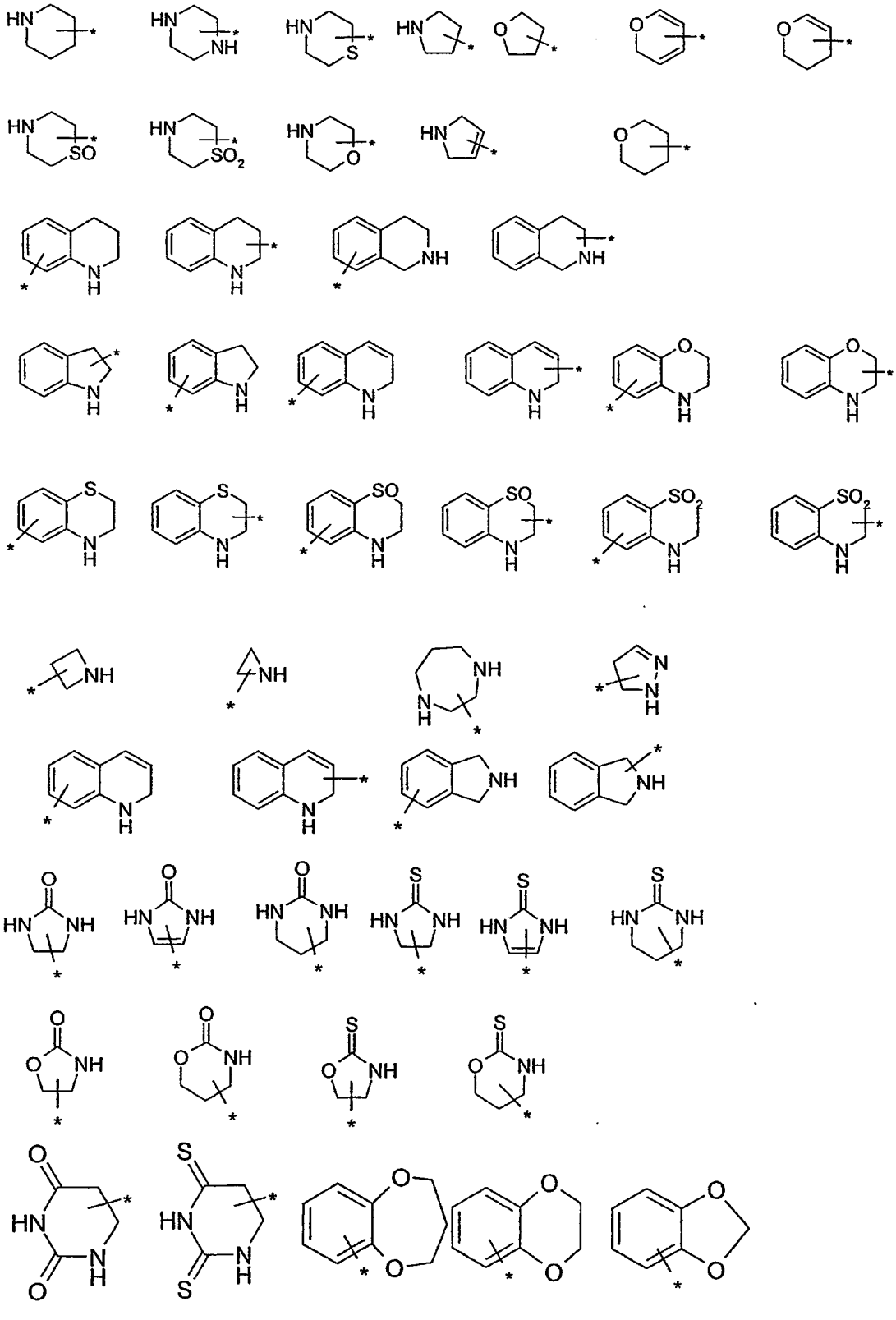
where any phenyl or naphthyl or mono- or bicyclic heterocyclyl (which mono- or bicyclic heterocyclyl is preferably as defined for mono- or bicyclic heterocyclyl, more preferably is selected from pyrrolyl, furanyl, tetrahydrofuranyl, tetrahydropyranyl and thienyl) mentioned as substituent of or as part of a substituent of substituted aryl is unsubstituted or substituted by one or more, preferably up to three, moieties independently selected from the group consisting of C_1-C_7-alkyl, C_1-C_7-alkenyl, C_1-C_7-alkynyl, halo-C_1-C_7-alkyl, such as trifluoromethyl, halo, especially fluoro, chloro, bromo or iodo, hydroxy, C_1-C_7-alkoxy, phenyloxy, naphthyloxy, phenyl- or naphthyl-C_1-C_7-alkoxy, C_1-C_7-alkanoyloxy, phenyl- or naphthyl-C_1-C_7-alkanoyloxy, amino, mono- or di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl, C_1-C_7-alkanoyl and/or phenyl- or naphthyl-C_1-C_7-alkanoyl)-amino, carboxy, C_1-C_7-alkoxycarbonyl, phenoxycarbonyl, naphthyloxycabonyl, phenyl-C_1-C_7-alkyloxycarbonyl, naphthyl-C_1-C_7-alkoxycarbonyl, carbamoyl, N-mono- or N,N-di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-aminocarbonyl, cyano, sulfo, sulfamoyl, N-mono- or N,N-di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-aminosulfonyl and nitro, or preferably, where preferred substituents are mentioned, by one or more of these mentioned substituents.Unsubstituted or substituted mono- or bicyclic heterocyclyl is a mono- or bicyclic heterocyclic moiety with an unsaturated, partially saturated or saturated ring system with preferably 3 to 22 (more preferably 3 to 14) ring atoms and with one or more, preferably one to four, heteroatoms independently selected from nitrogen (=N-, -NH- or substituted –NH-), oxygen and sulfur (-S-, S(=O)- or S-(=O)$_2$-) which is unsubstituted or substituted by one or more, e.g. up to three, substitutents preferably independently selected from the substitutents mentioned above for aryl and from oxo (=O) and thioxo (=S). Preferably, unsubstituted or substituted mono- or bicyclic heterocyclyl is selected from the following moieties:

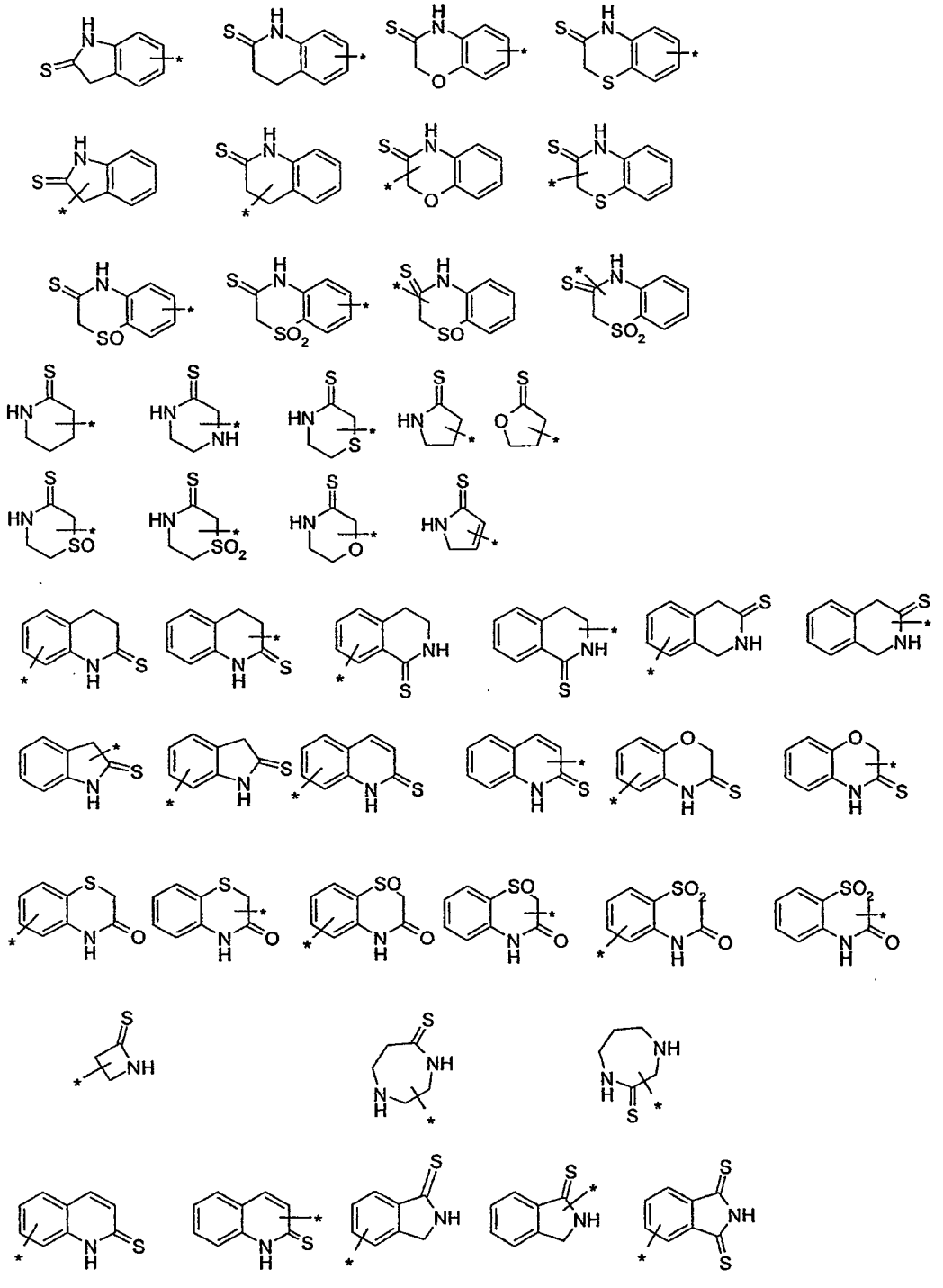


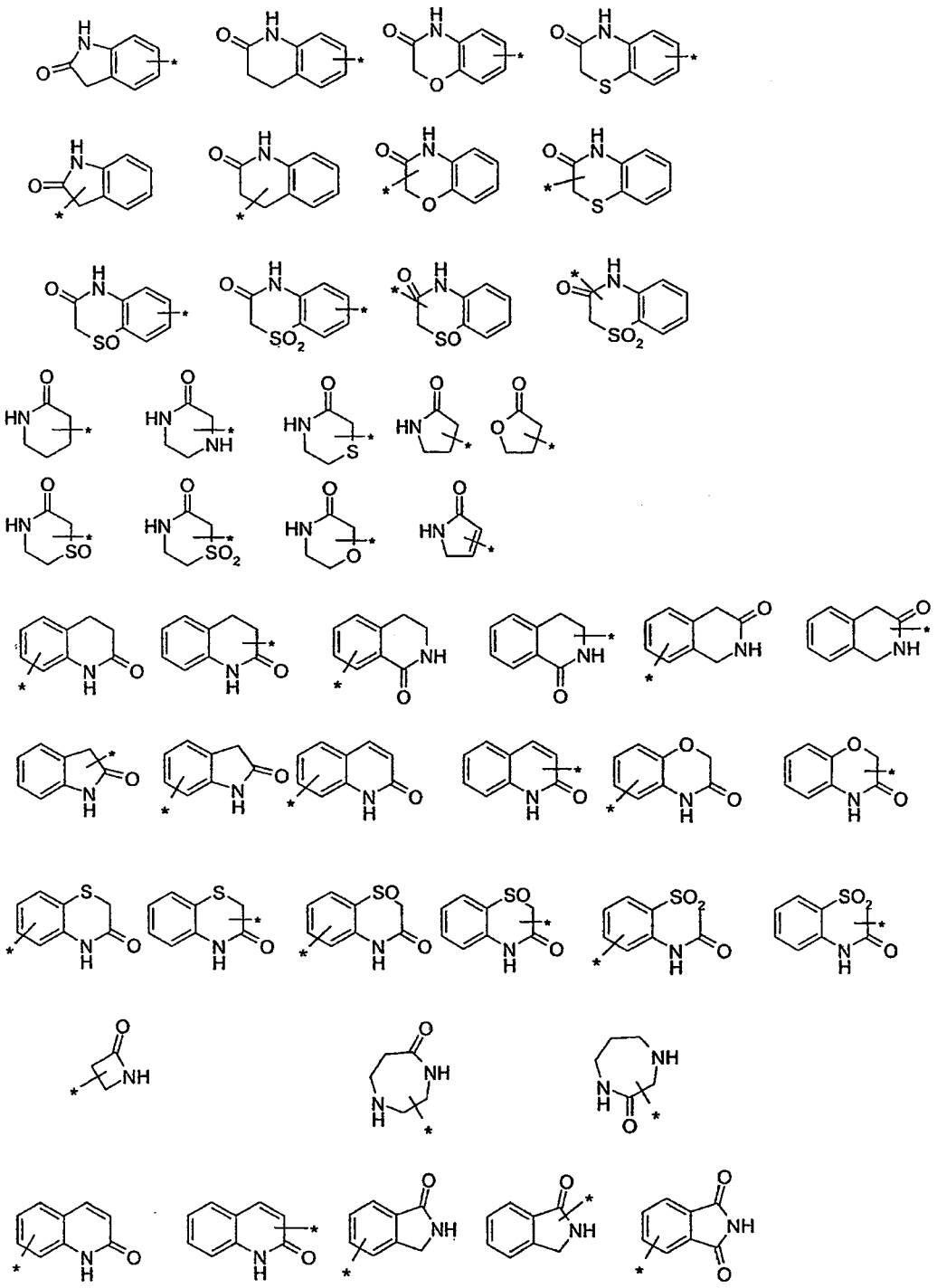












where in each case where an NH is present the bond with the asterisk connecting the respective heterocyclyl moiety to the rest of the molecule the H may be replaced with said

bond and/or the H may be replaced by a substituent (thus forming substituted imino), and one or more substituents may be present as just described.

Unsubstituted or substituted mono- or bicyclic cycloalkyl is preferably mono- or bicyclic, more preferably monocyclic, C_3-C_{16}, more preferably C_3-C_{10}-cycloalkyl, which may include one or more double (e.g. in cycloalkenyl) and/or triple bonds (e.g. in cycloalkinyl) with less double and/or triple bonds than required to form a fully unsaturated ring (e.g. aryl) system. Preferably, mono- or bicyclic cycloalkyl is saturated. The mono- or bicyclic cycloalkyl is unsubstituted or substituted by one or more, e.g. one to three substitutents preferably independently selected from those mentioned above as substituents for aryl.

In unsubstituted or substituted mono- or bicyclic aryl-alkyl or –C_1-C_7-alkyl, mono- or bicyclic aryl (which is preferably unsubstituted or substituted by one or more substituents, e.g. one to three substituents independently selected from those mentioned above as substituents for aryl) is preferably as described above for aryl and is bound to alkyl, preferably C_1-C_7-alkyl, either terminally or at any other carbon in the alkyl chain, e.g. at the 1-carbon; where the C_1-C_7-alkyl is otherwise unsubstituted or substituted as described below for unsubstituted or substituted alkyl and/or with unsubstituted or substituted mono- or bicyclic aryl as described above.

In unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl or –C_1-C_7-alkyl, mono- or bicyclic heterocyclyl is preferably as described above and is unsubstituted or substituted by one or more, e.g. up to three, substitutents independently selected from those mentioned above for substituted aryl, and heterocyclyl is bound to alkyl, preferably C_1-C_7-alkyl, either terminally or at any other carbon in the alkyl chain, e.g. at the 1-carbon; where the C_1-C_7-alkyl is otherwise unsubstituted or substituted as described below for unsubstituted or substituted alkyl and/or with unsubstituted or substituted mono- or bicyclic aryl as described above.

In unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or –C_1-C_7-alkyl, mono- or bicyclic cycloalkyl is preferably as described above and is unsubstituted or substituted by one or more, e.g. up to three, substitutents independently selected from those mentioned above for substituted aryl, and cycloalkyl is bound to alkyl, preferably C_1-C_7-alkyl, either terminally or at any other carbon in the alkyl chain, e.g. at the 1-carbon; where the C_1-C_7-

alkyl is otherwise unsubstituted or substituted as described below for unsubstituted or substituted alkyl and/or with unsubstituted or substituted mono- or bicyclic aryl as described above.

Acyl is preferably unsubstituted or substituted mono- or bicyclic aryl-carbonyl or -sulfonyl, unsubstituted or substituted mono- or bicyclic heterocyclylcarbonyl or -sulfonyl, unsubstituted or substituted mono- or bicyclic cycloalkylcarbonyl or -sulfonyl, formyl or (unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkyl or unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkyl)-carbonyl or -sulfonyl, or (especially if bound to N, S or O) unsubstituted or substituted alkyloxycarbonyl ,unsubstituted or substituted mono- or bicyclic aryl-oxycarbonyl, unsubstituted or substituted mono- or bicyclic heterocyclyloxycarbonyl, unsubstituted or substituted mono- or bicyclic cycloalkyloxycarbonyl, unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-oxycarbonyl , unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-oxycarbonyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-oxycarbonyl or N-mono- or N,N-di-(unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkyl and/or unsubstituted or substituted alkyl)-aminocarbonyl or -aminosulfonyl, with the proviso that–oxycarbonyl bound moieties are preferably bound to a nitrogen in the rest of the molecule. Examples of preferred acyl moieties other than R^1 and/or R^2 (e.g. R_a, R_b, R_c and/or R_d) are C_1-C_7-alkanoyl, (such as acetyl, 3,3-dimethyl-butyryl, 2,2-dimethyl-propionyl or 3,3-dimethyl-butyryl, unsubstituted (or mono-, di- or tri-(halo, C_1-C_7-alkoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyl and/or C_1-C_7-alkyl)-substituted)-phenyl-C_1-C_7-alkanoyl (e.g. the corresponding unsubstituted or substituted benzoyl or phenylacetyl) such as benzoyl or phenylacetyl, C_3-C_8-cycloalkyl-carbonyl or C_3-C_8-cycloalkyl-C_1-C_7-alkyl-carbonyll, such as cyclopropylcarbonyl, cyclobutylcarbonyl, cyclohexylacetyl or cyclohexylcarbonyl, (tetrahydrofuranyl or tetrahydropyranyl)-carbonyl or (tetrahydrofuranyl or tetrahydropyranyl)-C_1-C_7-alkyl-carbonyl, such as tetrahydrofuranyl-carbonyl, tetrahydropyranylcarbonyl, tetrahydrofuranylacetyl or tetrahydropyranylacetyl, unsubstituted or mono-, di- or tri-(halo and/or C_1-C_7-alkyl)-substituted) (phenyl- or phenyl-C_1-C_7-alkyl)-sulfonyl, such as phenylsulfonyl (= benzenesulfonyl) or phenylmethanesulfonyl, C_1-C_7-alkylsulfonyl, such as

methylsulfonyl (= methanesulfonyl), ((N-mono- or N,N-di-(C_1-C_7-alkyl)-aminocarbonyl, N-[phenyl or phenyl-C_1-C_7-alkyl (e.g. benzyl)]-aminocarbonyl, N-[C_3-C_8-cycloalkyl (e.g. cyclohexyl-), C_3-C_8-cycloalkyl-C_1-C_7-alkyl]aminocarbonyl, C_1-C_7-alkylaminocarbonyl or (C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl, napthyl-C_1-C_7-alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-C_1-C_7-alkyl and/or mono- or bicyclic heterocyclyl selected preferably from pyrrolyl, furanyl, thienyl (= thiophenyl), thiazolyl, pyrazolyl, triazolyl, tetrazolyl, oxetidinyl, 3-(C_1-C_7-alkyl)-oxetidinyl, pyridyl, pyrimidinyl, morpholino, thiomorpholino, piperidinyl, piperazinyl, pyrrolidinyl, tetrahydrofuran-onyl, tetrahydro-pyranyl, 1H-indazanyl, benzofuranyl, benzothiophenyl, (more preferably) isoquinolinyl, quinolinyl and indolyl)-oxycarbonyl, e.g. C_1-C_7-alkoxycarbonyl, such as tert-butyloxycarbonyl, isobutyloxycarbonyl or phenyl-C_1-C_7-alkyloxycarbonyl. As acyl R^1 or R^2, indolyl-C_1-C_7-alkanoyl, e.g. indolylcarbonyl, quinolyl-C_1-C_7-alkanoyl, e.g. quinolinylcarbonyl, or phenyl-C_1-C_7-alkanoyl, e.g. phenylacetyl, wherein indolyl, quinolyl and phenyl are unsubstituted or substituted by a substituent of the formula -(C_0-C_7-alkylene)-$(X)_r$-(C_1-C_7-alkylene)-$(Y)_s$-(C_0-C_7-alkylene)-H where C_0-alkylene means that a bond is present instead of bound alkylene, alkylene in each case may be straight-chained or branched and unsubstituted or (with lower preference) substituted e.g. by one or more moieties as defined for substituted alkyl, especially by halo, especially fluoro, hydroxy, C_1-C_7-alkoxy, phenyloxy, naphthyloxy, C_1-C_7-alkanoyloxy, benzoyloxy, naphthoyloxy, amino, mono- or di-(C_1-C_7-alkyl, C_1-C_7-alkanoyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-amino, carboxy, C_1-C_7-alkoxycarbonyl or cyano, r and s, each independently of the other, are 0 or 1 and each of X and Y, if present and independently of the others, is -O-, -NV-, -S-, -O-CO-, -CO-O-, -NV-CO-; -CO-NV-; -NV-SO_2-, -SO_2-NV; -NV-CO-NV-, -NV-CO-O-, -O-CO-NV-, -NV-SO_2-NV- wherein V is hydrogen or unsubstituted or substituted alkyl as defined below, especially C_1-C_7-alkyl, or is phenyl, naphthyl, phenyl- or naphthyl-C_1-C_7-alkyl or halo-C_1-C_7-alkyl; and optionally one or more, e.g. up to two, further substituents selected from the other substituents mentioned for substituted aryl. Unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl and unsubstituted or substituted mono- or bicyclic cycloalkyl are preferably as defined above whereever they are mentioned as part of acyl, unsubstituted or substituted alkyl is preferably as defined below.

Unsubstituted or substituted alkyl is preferably C_1-C_{20}-alkyl, more preferably C_1-C_7-alkyl, that is straight-chained or branched (one or, where appropriate, more times), which is unsubstituted or substituted by one or more, e.g. up to three moieties selected from

unsubstituted or substituted mono- or bicyclic heterocyclyl as described below, especially pyrrolyl, furanyl, thienyl (= thiophenyl), thiazolyl, pyrazolyl, triazolyl, tetrazolyl, oxetidinyl, 3-(C_1-C_7-alkyl)-oxetidinyl, pyridyl, pyrimidinyl, morpholino, thiomorpholino, piperidinyl, piperazinyl, pyrrolidinyl, tetrahydrofuran-onyl, tetrahydro-pyranyl, 1H-indazanyl, benzofuranyl, benzothiophenyl, , (more preferably) isoquinolinyl, quinolinyl or especially indolyl, each of which is unsubstituted or substituted as described above for unsubstituted or substituted heterocyclyl, e.g. by one to three substitutents independently selected from halo, hydroxy, such as chloro, C_1-C_7-alkyl, such as methyl, cyano and C_1-C_7-alkanoyl, such as acetyl; from unsubstituted or substituted mono- or bicyclic cycloalkyl as described above, especially cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl each of which is unsubstituted or substituted as described below for unsubstituted or substituted cycloalkyl; or especially from the group consisting of C_2-C_7-alkenyl, C_2-C_7-alkinyl, halo, hydroxy, C_1-C_7-alkoxy, halo-C_1-C_7-alkoxy, such as trifluoromethoxy, hydroxy-C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, phenyl- or naphthyloxy, phenyl- or naphthyl-C_1-C_7-alkyloxy, C_1-C_7-alkanoyloxy, (C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, phenyl and/or phenyl-C_1-C_7-alkyl)-aminocarbonyloxy, benzoyl- or naphthoyloxy, C_1-C_7-alkylthio, halo-C_1-C_7-alkthio, such as trifluoromethylthio, hydroxy-C_1-C_7-alkylthio, C_1-C_7-alkoxy-C_1-C_7-alkylthio, phenyl- or naphthylthio, phenyl- or naphthyl-C_1-C_7-alkylthio, nitro, amino, mono- or di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl and/or C_1-C_7-alkoxy-C_1-C_7-alkyl)-amino, C_1-C_7-alkanoylamino ****, benzoyl- or naphthoylamino**--**, C_1-C_7-alkylsulfonylamino, phenyl- or naphthylsulfonylamino), phenyl- or naphthyl-C_1-C_7-alkylsulfonylamino, phenyl- or naphthyl-C_1-C_7-alkylcarbonylamino, carboxyl, C_1-C_7-alkyl-carbonyl, C_1-C_7-alkoxy-carbonyl, phenyl- or naphthyloxycarbonyl, phenyl- or naphthyl-C_1-C_7-alkoxycarbonyl, carbamoyl, N-mono- or N,N-di-(C_1-C_7-alkyl)-aminocarbonyl, N-mono- or N,N-di-(naphthyl- or phenyl-C_1-C_7-alkyl)-aminocarbonyl, cyano, sulfenyl (-S-OH), sulfonyl (-S(=O)-OH), C_1-C_7-alkylsulfinyl (C_1-C_7-alkyl-S(=O)-), phenyl- or naphthylsulfinyl, phenyl- or naphthyl-C_1-C_7-alkylsulfinyl, sulfonyl, C_1-C_7-alkylsulfonyl, phenyl- or naphthylsulfonyl, phenyl- or naphthyl-C_1-C_7-alkylsulfonyl, sulfamoyl, N-mono or N,N-di-(C_1-C_7-alkyl, phenyl-, naphthyl, phenyl-C_1-C_7-alkyl or naphthyl-C_1-C_7-alkyl)-aminosulfonyl, N-mono-, N'-mono-, N,N-di- or N,N,N'-tri-(C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, phenyl and/or phenyl-C_1-C_7-alkyl)-aminocarbonylamino or –aminocarbonyloxy and N-mono-, N'-mono-, N,N-di- or N,N,N'-tri-(C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl and/or C_1-C_7-alkoxy-C_1-C_7-alkyl) aminosulfonylamino;

where any phenyl or naphthyl mentioned as substituent of or as part of a substituent of substituted alkyl is unsubstituted or substituted by one or more, preferably up to three,

moieties independently selected from the group consisting of C_1-C_7-alkyl, C_1-C_7-alkenyl, C_1-C_7-alkynyl, halo-C_1-C_7-alkyl, such as trifluoromethyl, halo, especially fluoro, chloro, bromo or iodo, hydroxy, C_1-C_7-alkoxy, phenyloxy, naphthyloxy, phenyl- or naphthyl-C_1-C_7-alkoxy, C_1-C_7-alkanoyloxy, phenyl- or naphthyl-C_1-C_7-alkanoyloxy, amino, mono- or di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl, C_1-C_7-alkanoyl and/or phenyl- or naphthyl-C_1-C_7-alkanoyl)-amino, carboxy, C_1-C_7-alkoxycarbonyl, phenoxycarbonyl, naphthyloxycabonyl, phenyl-C_1-C_7-alkyloxycarbonyl, naphthyl-C_1-C_7-alkoxycarbonyl, carbamoyl, N-mono- or N,N-di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-aminocarbonyl, cyano, sulfo, sulfamoyl, N-mono- or N,N-di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-aminosulfonyl and nitro, or preferably, where preferred substituents are mentioned, by one or more of these mentioned substituents.

Unsubstituted or substituted alkenyl is preferably C_2-C_{20}-alkenyl, more preferably C_2-C_7-alkenyl with one or, if possible, more double bonds, that is straight-chained or branched (one or, where appropriate, more times), which is unsubstituted or substituted by one or more, e.g. up to three moieties selected from those mentioned as substituents for substituted alkyl and from unsubstituted or substituted mono- or bicyclic aryl, each preferably as described above. Substituents with an active hydrogen (e.g. hydroxy or amino) are preferably present in the form of tautomers in equilibrium if bound directly to a carbon with a double bond, preferably at such positions substituents with active hydrogen are avoided.

Unsubstituted or substituted alkynyl is preferably C_2-C_{20}-alkynyl, more preferably C_2-C_7-alkynyl with one or, if possible, more triple bonds, that is straight-chained or branched (one or, where appropriate, more times), which is unsubstituted or substituted by one or more, e.g. up to three moieties selected from those mentioned as substituents for subsituted alkyl and from unsubsituted or substituted mono- or bicyclic aryl, each preferably as described above. Substituents with an active hydrogen (e.g. hydroxy or amino) are preferably present in the form of tautomers in equilibrium if bound directly to a carbon with a triple bond, preferably at such positions substituents with active hydrogen are avoided.

Esterified hydroxy is preferably acyloxy with acyl as defined above, more preferably C_1-C_7-alkanoyloxy or benzoyloxy.

Etherified hydroxy is preferably substituted C_1-C_7-alkyloxy wherein substituted alkyl is preferably as defined above, unsubstituted or substituted mono- or bicyclic aryloxy, unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyloxy, unsubstituted or substituted mono- or bicyclic heterocyclyloxy, unsubstituted or substituted mono- or bicyclic heterocyclyloxy-C_1-C_7-alkyloxy, unsubstituted or substituted mono- or bicyclic cycloalkyloxy or unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkyloxy (where in each case the moieties are preferably defined as above) or more preferably unsubstituted alkyloxy, especially C_1-C_7-alkyloxy.

Where an asterisk (*) marks a the bond binding a moiety, the corresponding bond is that shown in the corresponding formula of the respective compound of the formula I (or a precursor thereof) binding the respective moiety.

The preceding and especially the following preferred embodiments of the moieties and symbols in formula I can be employed independently of each other to replace more general definitions and thus to define specially preferred embodiments of the invention, where the remaining definitions can be kept broad as defined in embodiments of the inventions defined above of below.

Preferably, not more than one of R_1 and R_2 is acyl, the other has one of the meanings given hereinabove or hereinbelow for these moieties other than acyl.

As R^3, moieties of the formulae (a), (b), (c), (f) and slightly less (g), more preferably of the formulae (a), (b) or (f), are especially preferred.

The symbol m preferably stands for 0 or 2.

R_d preferably is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, or (if m = 2) is $-N(R_b)(R_c)$ wherein R_b and R_c are as defined above or below.

R_e is preferably hydrogen.

Preferably, at least one of R^4 and R^5 is hydrogen (i.e. the preferred compounds of the invention are (3,4-di-, 3,3,- tri, 3,4,4-tri-)substituted pyrrolidines), more preferably both are hydrogen.

In all definitions above and below the person having skill in the art will, without undue experimentation or considerations, be able to recognize which are relevant (e.g. those that if present provide compounds that are sufficiently stable for the manufacture of pharmaceuticals, e.g. having a half-life of more than 30 seconds) and thus are preferably encompassed by the present claims and that only chemically feasible bonds and substitutions (e.g. in the case of double or triple bonds, hydrogen carrying amino or hydroxy groups and the like) are encompassed, as well as tautomeric forms where present, especially in equilibrium. For example, preferably, for reasons of stability or chemical feasibility, directly vicinal atoms in chains preferably are not selected from oxy plus oxy, thio plus oxy, oxy plus thio or thio plus thio, except where ring systems or the like are present that are sufficiently stable. Substitutents binding via an O (e.g. in C_1-C_7-alkoxy) or S that is part of them are preferably not bound to nitrogen e.g. in rings.

Salts are especially the pharmaceutically acceptable salts of compounds of formula I. They can be formed where salt forming groups, such as basic or acidic groups, are present that can exist in dissociated form at least partially, e.g. in a pH range from 4 to 10 in aqueous solutions, or can be isolated especially in solid, especially crystalline, form.

Such salts are formed, for example, as acid addition salts, preferably with organic or inorganic acids, from compounds of formula I with a basic nitrogen atom (e.g. imino or amino), especially the pharmaceutically acceptable salts. Suitable inorganic acids are, for example, halogen acids, such as hydrochloric acid, sulfuric acid, or phosphoric acid. Suitable organic acids are, for example, carboxylic, phosphonic, sulfonic or sulfamic acids, for example acetic acid, propionic acid, lactic acid, fumaric acid, succinic acid, citric acid, amino acids, such as glutamic acid or aspartic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, benzoic acid, methane- or ethane-sulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 1,5-naphthalene-disulfonic acid, N-cyclohexylsulfamic acid, N-

methyl-, N-ethyl- or N-propyl-sulfamic acid, or other organic protonic acids, such as ascorbic acid.

In the presence of negatively charged radicals, such as carboxy or sulfo, salts may also be formed with bases, e.g. metal or ammonium salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium, magnesium or calcium salts, or ammonium salts with ammonia or suitable organic amines, such as tertiary monoamines, for example triethylamine or tri(2-hydroxyethyl)amine, or heterocyclic bases, for example N-ethyl-piperidine or N,N'-dimethylpiperazine.

When a basic group and an acid group are present in the same molecule, a compound of formula I may also form internal salts.

For isolation or purification purposes it is also possible to use pharmaceutically unacceptable salts, for example picrates or perchlorates. For therapeutic use, only pharmaceutically acceptable salts or free compounds are employed (where applicable comprised in pharmaceutical preparations), and these are therefore preferred.

In view of the close relationship between the compounds in free form and in the form of their salts, including those salts that can be used as intermediates, for example in the purification or identification of the compounds or salts thereof, any reference to "compounds", "starting materials" and "intermediates" hereinbefore and hereinafter, especially to the compound(s) of the formula I or their precursors, is to be understood as referring also to one or more salts thereof or a mixture of a corresponding free compound and one or more salts thereof, each of which is intended to include also any solvate, metabolic precursor such as ester or amide of the compound of formula I, or salt of any one or more of these, as appropriate and expedient and if not explicitly mentioned otherwise. Different crystal forms may be obtainable and then are also included.

Where the plural form is used for compounds, starting materials, intermediates, salts, pharmaceutical preparations, diseases, disorders and the like, this is intended to mean one (preferred) or more single compound(s), salt(s), pharmaceutical preparation(s), disease(s), disorder(s) or the like, where the singular or the indefinite article ("a", "an") is used, this is

intended to include the plural (for example also different configuration isomers of the same compound, e.g. enantiomers in racemates or the like) or preferably the singular ("one").

The compounds of the present invention can possess two or more asymmetric centers depending on the choice of the substituents. The preferred absolute configurations are as indicated herein specifically. However, any possible isolated or pure diastereoisomers, enantiomers or geometric enantiomers, and mixtures thereof, e.g., mixtures of enantiomers, such as racemates, are encompassed by the present invention.

As described above, the present invention provides in some of its important embodiments the use of (3,4-di-, 3,4,4-tri- or 3,3,4,4-tetra-)substituted pyrrolidine compounds for the preparation of a pharmaceutical formulation for the treatment of a disease that depends on activity of renin; the use of a compound of that class in the treatment of a disease that depends on activity of renin; compounds that are part of a subclass of these substituted pyrrolidine compounds for use in the diagnostic and therapeutic treatment of a warm-blooded animal, especially for the treatment of a disease (= disorder) that depends on activity of renin; new compounds that are part of a subclass of these substituted pyrrolidine compounds; pharmaceutical formulations comprising said substituted pyrrolidine compounds, and/or a method of treatment comprising administering said substituted pyrrolidine compounds, a method for the manufacture especially of said new substituted pyrrolidine compounds, as well as novel intermediates, starting materials and/or partial steps for their synthesis.

"Inappropriate" renin activity preferably relates to a state of a warm-blooded animal, especially a human, where renin shows a renin activity that is too high in the given situation (e.g. due to one or more of misregulation, overexpression e.g. due to gene amplification or chromosome rearrangement or infection by microorganisms such as virus that express an aberrant gene, abnormal activity e.g. leading to an erroneous substrate specificity or a hyperactive renin e.g. produced in normal amounts, too low activity of renin activity product removing pathways, high substrate concentration and/or the like) and/or leads to or supports a renin dependent disease or disorder as mentioned above and below, e.g. by too high renin activity. Such inappropriate renin activity may, for example, comprise a higher than normal activity, or further an activity in the normal or even below the normal range which, however, due to preceding, parallel and or subsequent processes, e.g. signaling, regulatory effect on

other processes, higher substrate or product concentration and the like, leads to direct or indirect support or maintenance of a disease or disorder, and/or an activity that supports the outbreak and/ or presence of a disease or disorder in any other way. The inappropriate activity of renin may or may not be dependent on parallel other mechanisms supporting the disorder or disease, and/or the prophylactic or therapeutic effect may or may include other mechanisms in addition to inhibition of renin. Therefore "dependent" has to be read as "dependent inter alia", (especially in cases where a disease or disorder is really exclusively dependent only on renin) preferably as "dependent mainly", more preferably as "dependent essentially only". A disease dependent on (especially inappropriate) activity of renin may also be one that simply responds to modulation of renin activity, especially responding in a beneficial way (e.g. lowering the blood pressure) in case of renin inhibition.

Where a disease or disorder dependent on inappropriate activity of a renin is mentioned (such in the definition of "use" in the following paragraph and also especially where a compound of the formula I is mentioned for use in the diagnostic or therapeutic treatment which is preferably the treatment of a disease or disorder dependent on inappropriate renin activity, this refers preferably to any one or more diseases or disorders that depend on inappropriate activity of natural renin and/or one or more altered or mutated forms thereof.

Where subsequently or above the term "use" is mentioned (as verb or noun) (relating to the use of a compound of the formula I or of a pharmaceutically acceptable salt thereof, or a method of use thereof), this (if not indicated differently or to be read differently in the context) includes any one or more of the following embodiments of the invention, respectively (if not stated otherwise): the use in the treatment of a disease or disorder that depends on (especially inappropriate) activity of renin, the use for the manufacture of pharmaceutical compositions for use in the treatment of a disease or disorder that depends on (especially inappropriate) activity of renin; a method of use of one or more compounds of the formula I in the treatment of a disease or disorder that depends on (especially inappropriate) activity of renin; a pharmaceutical preparation comprising one or more compounds of the formula I for the treatment of a disease or disorder that depends on (especially inappropriate) activity of renin; and one or more compounds of the formula I for use in the treatment of a disease or disorder in a warm-blooded animal, especially a human, preferably a disease that depends on (especially inappropriate) activity of renin; as appropriate and expedient, if not stated otherwise.

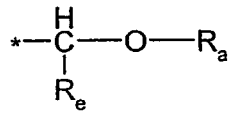
The terms "treat", "treatment" or "therapy" refer to the prophylactic (e.g. delaying or preventing the onset of a disease or disorder) or preferably therapeutic (including but not limited to preventive, delay of onset and/or progression, palliative, curing, symptom-alleviating, symptom-reducing, patient condition ameliorating, renin-modulating and/or renin-inhibiting) treatment of said disease(s) or disorder(s), especially of the one or more diseases or disorders mentioned above or below.

Preferred embodiments according to the invention

The groups of preferred embodiments of the invention mentionedin the claims and below are not to be regarded as exclusive, rather, e.g., in order to replace general expressions or symbols with more specific definitions, parts of those groups of compounds can be interchanged or exchanged using the definitions given above, or omitted, as appropriate, and each of the more specific definitions, independent of any others, may be introduced independently of or together with one or more other more specific definitions for other more general expressions or symbols.

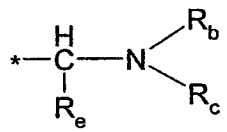
In a first preferred embodiment, the invention relates to a compound of the formula I wherein
R^1 is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, unsubstituted or substituted alkenyl, substituted or unsubstituted alkynyl or acyl;
R^2 is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, substituted monocyclic or (preferably) unsubstituted or substituted bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, unsubstituted or substituted alkenyl or substituted or unsubstituted alkynyl; with the proviso that if R^1 is one of the moieties mentioned in the definition of R^1 other than acyl then R^2 can also be unsubstituted (or substituted) monocyclic aryl-alkyl (meaning that in addition to the group of other moieties mentioned in the definition of R^2, the substituent R^2 can also be selected from unsubstituted monocyclic aryl-alkyl);
R^3 is a moiety selected from the group of moieties of the formulae

(a)

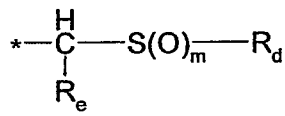


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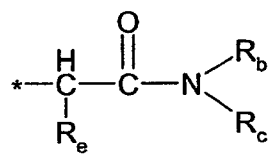
(b)



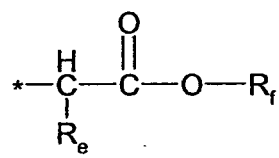
(c)



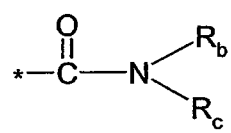
(d)



(e)

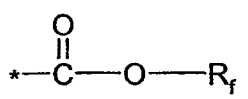


(f)



and

(g)



,

where in any of the moieties of the formulae given above under (a), (b), (c), (d), (e), (f) and (g) the asterisk (*) shows the bond binding the respective moiety R^3 to the rest of the molecule in formula I,

R_a is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted

mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, acyl or hydrogen;

R_b and R_c are independently selected from the group consisting of unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, acyl or hydrogen, with the proviso that preferably not more than one of R_b and R_c is acyl, and with the proviso that if R_c is one of the mentioned moieties other than acyl (meaning here and hereinafter that R_c is one of the moieties mentioned for R_b and R_c except for acyl, especially R_c = hydrogen or C_1-C_7-alkyl) then R_b can (as additional alternative to the other mentioned moieties) also be unsubstituted or substituted monocyclic aryl-alkyl;

Rd is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or (preferably if m is 0) acyl, or can have one of these meanings or can be $-N(R_b)(R_c)$ if m is 1 or preferably 2;

R_e is hydrogen, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or substituted or preferably unsubstituted C_1-C_7-alkyl; and

R_f is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl;

m is 0, 1 or 2;

each of R^4 and R^5 is selected, independently from the other, from hydrogen, unsubstituted or substituted alkyl, hydroxy or esterified or etherified hydroxy;

and T is methylene ($-CH_2-$) (preferred), methylene mono-substituted by alkyl (-[C(H)(alkyl)]-), carbonyl (-C(=O)-) (preferred) or thiocarbonyl (-C(=S)-);

or a pharmaceutically acceptable salt thereof,

for use in the (therapeutic or prophylactic) treatment of a mammal, especially a human, preferably of a disease that depends on the activity of renin, especially a disease that responds to inhibition of renin in a beneficial way, most preferably hypertension.

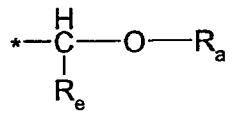
Regarding new compounds, the invention especially, in a still more preferred embodiment, relates to a compound of the formula I wherein

R^1 is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, unsubstituted or substituted alkenyl, substituted or unsubstituted alkynyl or acyl;

R^2 is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, unsubstituted or substituted alkenyl or substituted or unsubstituted alkynyl, with the proviso that if R^1 is one of the moieties mentioned in the definition of R^1 other than acyl then R^2 can also be unsubstituted or substituted monocyclic aryl-alkyl (meaning that in addition to the group of other moieties mentioned in the definition of R^2, the substituent R^2 can also be selected from unsubstituted monocyclic aryl-alkyl); ;

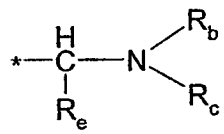
R^3 is a moiety selected from the group of moieties of the formulae

(a)

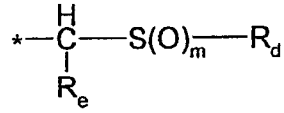


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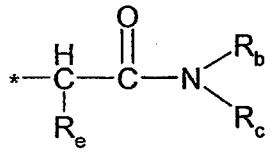
(b)



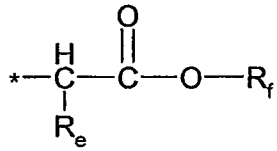
(c)



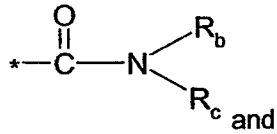
(d)



(e)

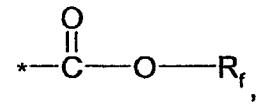


(f)



and

(g)



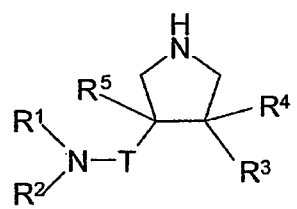
where in any of the moieties of the formulae given above under (a), (b), (c), (d), (e), (f) and (g) the asterisk (*) shows the bond binding the respective moiety R^3 to the rest of the molecule in formula I,

R_a is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, acyl or hydrogen;

R_b and R_c are independently selected from the group consisting of unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, acyl or hydrogen, with the proviso that preferably not more than one of R_b and R_c is acyl, and with the proviso that if R_c is one of the mentioned (in the definition of R_c in this paragraph) moieties other than acyl then R_b can also be unsubstituted or substituted monocyclic aryl-alkyl;

Rd in a moiety of the formulae (c) or (e) is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or (preferably if m is 0) acyl, or can have one of these meanings or can be $-N(R_b)(R_c)$ if m is 1 or preferably 2;
R_e is hydrogen (preferred), unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or substituted or preferably unsubstituted C_1-C_7-alkyl; and
R_f is substituted alkyl or preferably unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl;
m is 0, 1 or 2;
each of R^4 and R^5 is selected, independently from the other, from hydrogen, unsubstituted or substituted alkyl, hydroxy or esterified or etherified hydroxy;
and T is methylene ($-CH_2-$) (preferred), methylene mono-substituted by alkyl (-[C(H)(alkyl)]-), carbonyl (-C(=O)-) (preferred) or thiocarbonyl (-C(=S)-);
or a (preferably pharmaceutically acceptable) salt thereof.

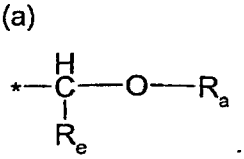
A compound of the formula I as such



(I)

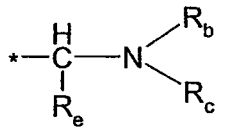
wherein
R^1 is acyl;
R^2 is unsubstituted or substituted alkyl,
R^3 is a moiety selected from the group of moieties of the formulae

(a)

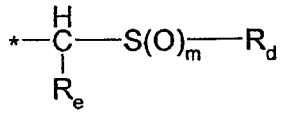


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(b)

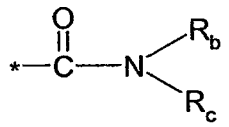


(c)



and

(f)



where in any of the moieties of the formulae given above under (a), (b), (c) and (f) the asterisk (*) shows the bond binding the respective moiety R^3 to the rest of the molecule in formula I, more preferably selected from the moieties of the formula (a), (b) or (f);

R_a is acyl or hydrogen;

R_b is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl or acyl;

R_c is hydrogen, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkyloxy-C_1-C_7-alkyl or preferably C_3-C_8-cycloalkyl or C_1-C_7-alkyl;

R_d is unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl or -$N(R_b)(R_c)$;

R_e is hydrogen or C_1-C_7-alkyl; and

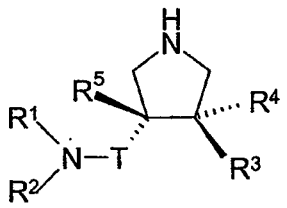
m is 2;

each of R^4 and R^5 is selected, independently from the other, from hydrogen, unsubstituted or substituted alkyl, hydroxy or esterified or etherified hydroxy; where preferably at least one, more preferably both of R^4 and R^5 are hydrogen;

and T is methylene (-CH_2-) (preferred), methylene mono-substituted by alkyl (-[C(H)(alkyl)]-), carbonyl (-C(=O)-) (preferred) or thiocarbonyl (-C(=S)-);

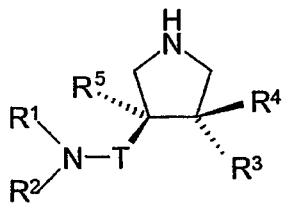
or an (especially pharmaceutically acceptable) salt thereof, is one further preferred embodiment of the invention.

Highly preferably, a compound of the formula I in the preceding and subsequent embodiments (be it use, compound for use or new compound) is of the formula IA with the following configuration:



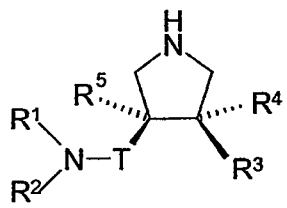
(IA);

Alternatively and defining a still preferred embodiment of the invention; a compound of the formula I in the preceding and subsequent embodiments (be it use, compound for use or new compound) can be of the formula IB with the following configuration:



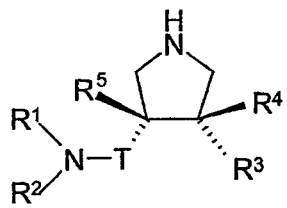
(IB)

Alternatively and defining a still preferred embodiment of the invention, a compound of the formula I in the preceding and subsequent embodiments (be it use, compound for use or new compound) can be of the formula IC with the following configuration:



(IC)

Alternatively and defining a still preferred embodiment of the invention; a compound of the formula I in the preceding and subsequent embodiments (be it use, compound for use or new compound) can be of the formula ID with the following configuration:



(ID)

In each of the formulae IA, IB, IC and ID, the moieties R^1, R^2, R^3, R^4, R^5 and L are as defined hereinbefore or preferably hereinafter for the respective more general or especially more preferred embodiments of the invention.

The formula IA, IB, IC or ID can replace formula I wherever a compound of the formula I (including a salt thereof) is mentioned hereinbefore or hereinafter; also, the corresponding intermediates are preferred.

A further preferred embodiment of the invention relates to the use of a compound of the formula I wherein

R^1 is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, unsubstituted or substituted alkenyl, substituted or unsubstituted alkynyl or acyl;
R^2 is unsubstituted or substituted mono- or bicyclic aryl-alkyl;
R^3 is a moiety selected from the group of moieties of the formulae (a), (b), (c), (d), (e), (f) or (g), more preferably of the formulae (a), (b), (c) and (f), still more preferably of the formulae (a), (b) or (f), given in the first description of a compound of the formula I in this disclosure; where in any of the moieties of these moiety formulae the asterisk (*) shows the bond binding the respective moiety R^3 to the rest of the molecule in formula I,
R_a is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, acyl or hydrogen;
R_b and R_c are independently selected from the moieties given under R_a, with the proviso that preferably not more than one of R_b and R_c is acyl,
Rd is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono-

or bicyclic cycloalkyl-alkyl or (preferably if m is 0) acyl, or can have one of these meanings or can be -N(R_b)(R_c) if m is 1 or preferably 2;
R_e is unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or substituted or preferably unsubstituted C_1-C_7-alkyl or hydrogen; and
R_f is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl;
m is 0, 1 or 2, preferably 0 or more preferably 2;
each of R^4 and R^5 is selected, independently from the other, from hydrogen, unsubstituted or substituted alkyl, hydroxy or esterified or etherified hydroxy;
and T is methylene (-CH_2-), methylene mono-substituted by alkyl (-[C(H)(alkyl)]-) , carbonyl (-C(=O)-) or thiocarbonyl (-C(=S)-);
or a pharmaceutically acceptable salt thereof,
in the preparation of a pharmaceutical formulation for the treatment of a disease that depends on activity of renin, especially hypertension; or in the treatment of a disease that depends on activity of renin, especially hypertension.

Another preferred embodiment of the invention relates to the use of a compound of the formula I, wherein, R^1 is phenyl, naphthyl, mono- or bicyclic heterocyclyl, phenylcarbonyl, phenylacetyl, naphthylcarbonyl, naphthylacetyl, mono- or bicyclic heterocyclylcarbonyl or -acetyl, phenylsulfonyl, naphthylsulfonyl or mono- or bicyclic heterocyclylsulfonyl; wherein mono- or bicyclic heterocyclyl is pyrrolyl, furanyl, thienyl (= thiophenyl), thiazolyl, pyrazolyl, triazolyl, tetrazolyl, oxetidinyl, 3-(C_1-C_7-alkyl)-oxetidinyl, pyridyl, pyrimidinyl, morpholino, thiomorpholino, piperidinyl, piperazinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrofuran-onyl, tetrahydro-pyranyl, 1H-indazolyl, benzofuranyl, benzothiophenyl, or more preferably isoquinolyl, quinolyl or especially indolyl, and each such mono- or bicyclic heterocyclyl, phenyl or naphthyl mentioned under R^1 is unsubstituted or preferably substituted by one or more, especially one to three, moieties, preferably independently selected from the group consisting of
(i) a substituent of the formula -(C_0-C_7-alkylene)-$(X)_r$-(C_1-C_7-alkylene)-$(Y)_s$-(C_0-C_7-alkylene)-H (especially in substituted aryl or substituted aryl-alkyl as R^1) where C_0-alkylene means that a

bond is present instead of bound alkylene, alkylene in each case may be straight-chained or branched and unsubstituted or (with lower preference) substituted e.g. by one or more moieties as defined for substituted alkyl, especially by halo, especially fluoro, hydroxy, C_1-C_7-alkoxy, phenyloxy, naphthyloxy, C_1-C_7-alkanoyloxy, benzoyloxy, naphthoyloxy, amino, mono- or di-(C_1-C_7-alkyl, C_1-C_7-alkanoyl, phenyl-C_1-C_7-alkanoyl, naphthyl-C_1-C_7-alkanoyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-amino, carboxy, C_1-C_7-alkoxycarbonyl or cyano, r and s, each independently of the other, are 0 or 1 and each of X and Y, if present and independently of the others, is -O-, -NV-, -S-, -O-CO-, -CO-O-, -NV-CO-; -CO-NV-; -NV-SO_2-, -SO_2-NV; -NV-CO-NV-, -NV-CO-O-, -O-CO-NV-, -NV-SO_2-NV- wherein V is hydrogen or unsubstituted or substituted alkyl as defined below, especially C_1-C_7-alkyl, or is phenyl, naphthyl, phenyl- or naphthyl-C_1-C_7-alkyl or halo-C_1-C_7-alkyl; e.g. C_1-C_7-alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl or tert-butyl, halo-C_1-C_7-alkyl, such as trifluoromethyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, such as 3-methoxypropyl or 2-methoxyethyl, C_1-C_7-alkoxy-C_1-C_7-alkoxy-C_1-C_7-alkyl, phenyloxy- or naphthyloxy-C_1-C_7-alkyl, C_1-C_7-alkanoyloxy-C_1-C_7-alkyl, amino-C_1-C_7-alkyl, such as aminomethyl, C_1-C_7-alkoxy-C_1-C_7-alkylamino-C_1-C_7-alkyl, mono- or di- (C_1-C_7-alkyl-, naphthyl-, phenyl, naphthyl-C_1-C_7-alkyl and/or phenyl-C_1-C_7-alkyl)-amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino-C_1-C_7-alkyl, C_1-C_7-alkyl-O-CO-NH-C_1-C_7-alkyl, C_1-C_7-alkylsulfonylamino-C_1-C_7-alkyl, C_1-C_7-alkyl-NH-CO-NH-C_1-C_7-alkyl, C_1-C_7-alkyl-NH-SO_2-NH-C_1-C_7-alkyl, C_1-C_7-alkoxy, hydroxy-C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, C_1-C_7-alkanoyloxy, halo-C_1-C_7-alkoxy, such as trifluoromethoxy, phenyl- or naphthyl-C_1-C_7-alkanoyloxy, phenyl- or naphthyl-C_1-C_7-alkylaminocarbonyloxy, halo-C_1-C_7-alkylthio, such as trifluoromethylthio, phenyl- or naphthyl-C_1-C_7-alkylthio, mono- or di-(C_1-C_7-alkyl-, naphthyl-C_1-C_7-alkyl-, phenyl-C_1-C_7-alkyl- and/or C_1-C_7-alkoxy-C_1-C_7-alkyl-)amino, C_1-C_7-alkanoylamino, C_1-C_7-alkylsulfonylamino, phenyl- or naphthyl-C_1-C_7-alkanoylamino, phenyl- or naphthyl-C_1-C_7-alkylaminocarbonyl-amino, carboxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-carbonyl, hydroxy-C_1-C_7-alkoxycarbonyl, C_1-C_7-alkoxy-C_1-C_7-alkoxycarbonyl, amino-C_1-C_7-alkoxycarbonyl, (N-) mono-(C_1-C_7-alkyl)-amino-C_1-C_7-alkoxycarbonyl, C_1-C_7-alkanoylamino-C_1-C_7-alkoxycarbonyl, N- mono- or N,N-di-(C_1-C_7-alkyl, naphthyl-C_1-C_7.alkyl and/ or phenyl-C_1-C_7-alkyl)-aminocarbonyl, C_1-C_7-alkylsulfonyl, halo-C_1-C_7-alkylsulfonyl, hydroxy-C_1-C_7-alkylsulfonyl, C_1-C_7-alkoxy-C_1-C_7-alkylsulfonyl, amino-C_1-C_7-alkylsulfonyl, N-mono- or di-(C_1-C_7-alkyl)-amino-C_1-C_7-alkylsulfonyl, C_1-C_7-alkanoylamino-C_1-C_7-alkylsulfonyl, N-C_1-C_7-alkoxy-C_1-C_7-alkylcarbamoyl or N-mono- or N,N-di-(C_1-C_7-alkyl)-aminosulfonyl,

(ii) from C_2-C_7-alkenyl, C_2-C_7-alkynyl, phenyl, naphtyl, mono- or bicyclic heterocyclyl, especially as defined below for mono- or bicyclic heterocyclyl, preferably selected from pyrrolyl, furanyl, thienyl, pyrimidine-2,4-dione-1-, -3- or –5-yl, tetrahydropyranyl and tetrahydrofuranyl, phenyl- or naphthyl- or (mono- or bicyclic heterocyclyl)-C_1-C_7-alkyl or C_1-C_7-alkyloxy wherein mono- or bicyclic heterocyclyl is as defined below, preferably selected from pyrrolyl, furanyl, tetrahydrofuranyl, tetrahydropyranyl and thienyl; such as benzyl or naphthylmethyl, tetrahydrofuranyl- or tetrahydropyranyl-C_1-C_7-alkyloxycarbonyl, benzoyl- or naphthoylamino-C_1-C_7-alkyl, (phenyl- or naphthyl- or mono- or bicyclic heterocyclyl)-sulfonylamino-C_1-C_7-alkyl wherein phenyl or naphthyl or mono- or bicyclic heterocyclyl is unsubstituted or substituted, preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkylsulfonylamino-C_1-C_7-alkyl, halo, hydroxy, phenyl-C_1-C_7-alkoxy wherein phenyl is preferably unsubstituted or substituted, preferably by C_1-C_7-alkoxy and/or halo, mono- or bicyclic heterocyclyl-C_1-C_7-alkoxy, (mono- or bicyclic heterocyclyl or phenyl or naphthyl)-oxy, naphthyl-C_1-C_7-alkyloxy, benzoyl or naphthoyl or mono- or bicyclic heterocyclylcarbonyl)-oxy, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)- aminocarbonyloxy, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-thio, (benzoyl or naphthoyl or mono- or bicyclic heterocyclyl)-thio, nitro, amino, di-((naphthyl or phenyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkyl)-amino, (benzoyl or naphthoyl or mono- or bicyclic heterocyclyl)-amino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-sulfonylamino wherein phenyl or naphthyl is unsubstituted or substituted preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkylsulfonylamino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-aminocarbonylamino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-oxycarbonylamino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkyloxycarbonylamino, carboxyl, C_1-C_7-alkyl-carbonyl, halo-C_1-C_7-alkylcarbonyl, hydroxy-C_1-C_7-alkylcarbonyl, C_1-C_7-alkoxy-C_1-C_7-alkylcarbonyl, amino-C_1-C_7-alkylcarbonyl, (N-) mono- or (N,N-) di-(C_1-C_7-alkyl)-amino-C_1-C_7-alkylcarbonyl, C_1-C_7-alkanoylamino-C_1-C_7-alkylcarbonyl, halo-C_1-C_7-alkoxycarbonyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-oxy-carbonyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkoxycarbonyl, (N,N-) di-(C_1-C_7-alkyl)-amino-C_1-C_7-alkoxycarbonyl, carbamoyl, N-mono or N,N-di-(naphthyl or phenyl or mono- or bicyclic heterocyclyl)-aminocarbonyl, cyano, C_1-C_7-alkylene which is unsubstituted or substituted by up to four C_1-C_7-alkyl substituents and bound to two adjacent ring atoms of the aryl moiety, sulfenyl, sulfinyl, C_1-C_7-alkylsulfinyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-sulfinyl wherein phenyl or naphthyl is unsubstituted or

substituted preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, phenyl- or naphthyl-C_1-C_7-alkylsulfinyl, sulfonyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-sulfonyl wherein phenyl or naphthyl is unsubstituted or substituted preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkylsulfonyl, sulfamoyl and N-mono or N,N-di-(C_1-C_7-alkyl, phenyl-, naphthyl, mono- or bicyclic heterocyclyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl and/or mono- or bicyclic heterocyclyl-C_1-C_7-alkyl)-aminosulfonyl;

where any phenyl or naphthyl or mono- or bicyclic heterocyclyl - which mono- or bicyclic heterocyclyl is preferably as defined for mono- or bicyclic heterocyclyl, more preferably is selected from pyrrolyl, furanyl, tetrahydrofuranyl, tetrahydropyranyl and thienyl - mentioned as substituent of or as part of a substituent of mono- or bicyclic heterocyclyl, phenyl or naphthyl R^1 under (i) or (ii) is unsubstituted or substituted by one or more, preferably up to three, moieties independently selected from the group consisting of C_1-C_7-alkyl, C_1-C_7-alkenyl, C_1-C_7-alkynyl, halo-C_1-C_7-alkyl, such as trifluoromethyl, halo, especially fluoro, chloro, bromo or iodo, hydroxy, C_1-C_7-alkoxy, phenyloxy, naphthyloxy, phenyl- or naphthyl-C_1-C_7-alkoxy, C_1-C_7-alkanoyloxy, phenyl- or naphthyl-C_1-C_7-alkanoyloxy, amino, mono- or di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl, C_1-C_7-alkanoyl and/or phenyl- or naphthyl-C_1-C_7-alkanoyl)-amino, carboxy, C_1-C_7-alkoxycarbonyl, phenoxycarbonyl, naphthyloxycabonyl, phenyl-C_1-C_7-alkyloxycarbonyl, naphthyl-C_1-C_7-alkoxycarbonyl, carbamoyl, N-mono- or N,N-di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-aminocarbonyl, cyano, sulfo, sulfamoyl, N-mono- or N,N-di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-aminosulfonyl and nitro, or preferably, where preferred substituents are mentioned, by one or more of these mentioned substituents;

R^2 is phenyl, naphthyl, phenyl-C_1-C_7-alkyl or naphthyl-C_1-C_7-alkyl, wherein each phenyl or naphthyl mentioned so far in the definition of R^2 is unsubstituted or substituted as just described for substituted phenyl or naphthyl in the definition of R^1,

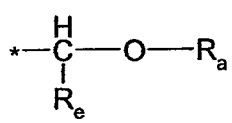
or is preferably C_1-C_7-alkyl that is unsubstituted or substituted by one or more, especially up to three, e.g. one or two, substituents independently selected from the group consisting of C_2-C_7-alkenyl, C_2-C_7-alkinyl, halo, hydroxy, C_1-C_7-alkoxy, halo-C_1-C_7-alkoxy, such as trifluoromethoxy, hydroxy-C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, phenyl- or naphthyloxy, phenyl- or naphthyl-C_1-C_7-alkyloxy, C_1-C_7-alkanoyloxy, (C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, phenyl and/or phenyl-C_1-C_7-alkyl)-aminocarbonyloxy, benzoyl- or

naphthoyloxy, C_1-C_7-alkylthio, halo-C_1-C_7-alkthio, such as trifluoromethylthio, hydroxy-C_1-C_7-alkylthio, C_1-C_7-alkoxy-C_1-C_7-alkylthio, phenyl- or naphthylthio, phenyl- or naphthyl-C_1-C_7-alkylthio, nitro, amino, mono- or di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl and/or C_1-C_7-alkoxy-C_1-C_7-alkyl)-amino, C_1-C_7-alkanoylamino, benzoyl- or naphthoylamino, phenyl- or naphthyl-C_1-C_7-alkylcarbonylamino, C_1-C_7-alkylsulfonylamino, phenyl- or naphthylsulfonylamino wherein phenyl or naphthyl is unsubstituted or substituted by one or more, especially one to three, C_1-C_7-alkyl moieties, phenyl- or naphthyl-C_1-C_7-alkylsulfonylamino, carboxyl, C_1-C_7-alkyl-carbonyl, C_1-C_7-alkoxy-carbonyl, phenyl- or naphthyloxycarbonyl, phenyl- or naphthyl-C_1-C_7-alkoxycarbonyl, carbamoyl, N- mono- or N,N-di-(C_1-C_7-alkyl)-aminocarbonyl, N-mono- or N,N-di-(naphthyl- or phenyl-C_1-C_7-alkyl)-aminocarbonyl, cyano, sulfenyl (-S-OH), sulfonyl (-S(=O)-OH), C_1-C_7-alkylsulfinyl (C_1-C_7-alkyl-S(=O)-), phenyl- or naphthylsulfinyl wherein phenyl or naphthyl is unsubstituted or substituted by one or more, especially one to three, C_1-C_7-alkyl moieties, phenyl- or naphthyl-C_1-C_7-alkylsulfinyl, sulfonyl, C_1-C_7-alkylsulfonyl, phenyl- or naphthylsulfonyl wherein phenyl or naphthyl is unsubstituted or substituted by one or more, especially one to three, C_1-C_7-alkyl moieties, phenyl- or naphthyl-C_1-C_7-alkylsulfonyl, sulfamoyl, N-mono or N,N-di-(C_1-C_7-alkyl, phenyl-, naphthyl, phenyl-C_1-C_7-alkyl or naphthyl-C_1-C_7-alkyl)-aminosulfonyl, N-mono-, N'-mono-, N,N-di- or N,N,N'-tri-(C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, phenyl and/or phenyl-C_1-C_7-alkyl)-aminocarbonylamino or –aminocarbonyloxy and N-mono-, N'-mono-, N,N-di- or N,N,N'-tri-(C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl and/or C_1-C_7-alkoxy-C_1-C_7-alkyl) aminosulfonylamino;

or C_3-C_{10}-cycloalkyl or C_3-C_{10}-cycloalkyl-C_1-C_7-alkyl;

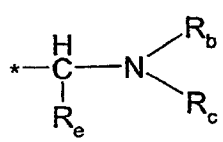
R^3 is a moiety selected from the group of moieties of the formulae

(a)

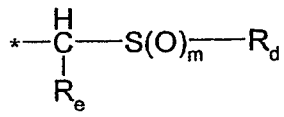


;

(b)

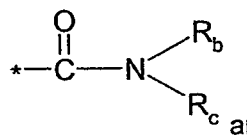


(c)



and

(f)



and

where in any of the moieties of the formulae given above under (a), (b), (c) and (f) the asterisk (*) shows the bond binding the respective moiety R^3 to the rest of the molecule in formula I,

R_a is acyl selected from the group consisting of C_1-C_7-alkanoyl, such as acetyl, 3,3-dimethyl-butyryl, 2,2-dimethyl-propionyl or 3,3-dimethyl-butyryl, unsubstituted (or with lower preference) mono-, di- or tri-(halo C_1-C_7-alkoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyl and/or C_1-C_7-alkyl)-substituted) phenyl-C_1-C_7-alkanoyl, C_3-C_8-cycloalkylcarbonyl or C_3-C_8-cycloalkyl-C_1-C_7-alkyl-carbonyl, such as cyclopropylcarbonyl, cyclobutylcarbonyl, cyclohexylacetyl or cyclohexylcarbonyl, (tetrahydrofuranyl or tetrahydropyranyl)-carbonyl or (tetrahydrofuranyl or tetrahydropyranyl)-C_1-C_7-alkyl-carbonyl, such as tetrahydrofuranyl-carbonyl, tetrahydropyranylcarbonyl, tetrahydrofuranylacetyl or tetrahydropyranylacetyl, , N-mono- or N,N-di-(C_1-C_7-alkyl)-aminocarbonyl, N-[phenyl or phenyl-C_1-C_7-alkyl (e.g. benzyl)]-aminocarbonyl, N-[C_3-C_8-cycloalkyl (e.g. cyclohexyl-) or C_3-C_8-cycloalkyl-C_1-C_7-alkyl]aminocarbonyl, C_1-C_7-alkylaminocarbonyl, or (C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or napthyl-C_1-C_7-alkyl)-oxycarbonyl, e.g. C_1-C_7-alkoxycarbonyl, such as tert-butyloxycarbonyl or isobutyloxycarbonyl, or phenyl-C_1-C_7-alkyloxycarbonyl; or is hydrogen;

R_b is C_1-C_7-alkyl or – in each case unsubstituted or substituted - phenyl, naphthyl, phenyl-C_1-C_7-alkyl or naphthyl-C_1-C_7-alkyl wherein in the case of a substituted moiety the substituents are one or more, especially up to three, substituents independently selected from the group consisting of C_1-C_7-alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl or tert-butyl, C_2-C_7-alkenyl, C_2-C_7-alkinyl, hydroxy-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, such as trifluoromethyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, such as 3-methoxypropyl or 2-methoxyethyl, amino-C_1-C_7-alkyl, C_1-C_7-alkoxy, hydroxy-C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, C_1-C_7-alkanoyloxy, amino, mono- or di-(C_1-C_7-alkyl)-amino, C_1-C_7-alkanoylamino, C_1-C_7-alkylsulfonylamino, C_1-C_7-alkoxy-carbonyl, carboxy-C_1-C_7-alkyl, halo, hydroxy, halo-C_1-C_7-alkoxy, such as trifluoromethoxy, halo-C_1-C_7-alkylthio, such as trifluoromethylthio, nitro, carboxyl, C_1-C_7-alkyl-carbonyl, halo-C_1-C_7-alkylcarbonyl, hydroxy-C_1-C_7-alkylcarbonyl, C_1-C_7-

alkoxy-C_1-C_7-alkylcarbonyl, halo-C_1-C_7-alkoxycarbonyl, carbamoyl, cyano, C_1-C_7-alkylsulfinyl, sulfonyl, C_1-C_7-alkylsulfonyl, halo-C_1-C_7-alkylsulfonyl, hydroxy-C_1-C_7-alkylsulfonyl, C_1-C_7-alkoxy-C_1-C_7-alkylsulfonyl, sulfamoyl and N-mono or N,N-di-(C_1-C_7-alkyl) -aminosulfonyl; or is acyl as just defined under R_a or selected from unsubstituted or mono-, di- or tri-(halo and/or C_1-C_7alkyl)-substituted (phenyl or phenyl-C_1-C_7-alkyl)-sulfonyl, such as phenylsulfonyl or phenylmethanesulfonyl, or C_1-C_7-alkylsulfonyl, such as methanesulfonyl;
R_c is hydrogen, C_1-C_7-alkyl, C_3-C_8-cycloalkyl, hydroxy-C_1-C_7-alkyl or C_1-C_7-alkyloxy-C_1-C_7-alkyl, preferably hydrogen or C_1-C_7-alkyl;
R_d is unsubstituted or substituted phenyl- or naphthyl-C_1-C_7-alkyl wherein in the case of a substituted moiety the substituents are one or more, especially up to three, substituents independently selected from those mentioned for unsubstituted of substituted phenyl- or naphthyl-C_1-C_7-alkyl under R_b, or is -N(R_b)(R_c);
R_e is C_1-C_7-alkyl or preferably hydrogen; and
m is 2;

each of R^4 and R^5 is selected, independently from the other, from C_1-C_7-alkyl, hydroxy, C_1-C_7-alkyloxy and preferably hydrogen;
and T is carbonyl or preferably methylene;

or a pharmaceutically acceptable salt thereof, for the treatment of a disease that depends on activity of renin, especially hypertension, or preferably for the manufacture of a pharmaceutical formulation for the treatment of a disease that depends on activity of renin, especially hypertension.

A quite preferred embodiment of the invention relates to a new compound of the formula I, wherein
R^1, R^3, R^4, R^5, m and T are as defined in the preceding paragraph and
R^2 is phenyl, naphthyl or (with lower preference) naphthyl-C_1-C_7-alkyl, wherein each phenyl or naphthyl mentioned so far in the definition of R^2 is unsubstituted or substituted as just described for substituted phenyl or naphthyl in the definition of R^1, or preferably C_1-C_7-alkyl that is unsubstituted or substituted by one or more, especially up to three, e.g. one or two, substituents independently selected from the group consisting of C_2-C_7-alkenyl, C_2-C_7-alkinyl, halo, hydroxy, C_1-C_7-alkoxy, halo-C_1-C_7-alkoxy, such as trifluoromethoxy, hydroxy-C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, phenyl- or naphthyloxy, phenyl- or naphthyl-C_1-C_7-

alkyloxy, C_1-C_7-alkanoyloxy, benzoyl- or naphthoyloxy, C_1-C_7-alkylthio, halo-C_1-C_7-alkthio, such as trifluoromethylthio, hydroxy-C_1-C_7-alkylthio, C_1-C_7-alkoxy-C_1-C_7-alkylthio, phenyl- or naphthylthio, phenyl- or naphthyl-C_1-C_7-alkylthio, C_1-C_7-alkanoylthio, benzoyl- or naphthoylthio, nitro, amino, mono- or di-(C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl and/or C_1-C_7-alkoxy-C_1-C_7-alkyl)-amino, mono- or di-(naphthyl- or phenyl-C_1-C_7-alkyl)-amino, C_1-C_7-alkanoylamino, benzoyl- or naphthoylamino, C_1-C_7-alkylsulfonylamino, phenyl- or naphthylsulfonylamino wherein phenyl or naphthyl is unsubstituted or substituted by one or more, especially one to three, C_1-C_7-alkyl moieties, phenyl- or naphthyl-C_1-C_7-alkylsulfonylamino, carboxyl, C_1-C_7-alkyl-carbonyl, C_1-C_7-alkoxy-carbonyl, phenyl- or naphthyloxycarbonyl, phenyl- or naphthyl-C_1-C_7-alkoxycarbonyl, carbamoyl, N- mono- or N,N-di-(C_1-C_7-alkyl)-aminocarbonyl, N-mono- or N,N-di-(naphthyl- or phenyl-C_1-C_7-alkyl)-aminocarbonyl, cyano, sulfenyl, (-S-OH) sulfonyl (-S(=O)-OH), C_1-C_7-alkylsulfinyl (C_1-C_7-alkyl-S(=O)-), phenyl- or naphthylsulfinyl wherein phenyl or naphthyl is unsubstituted or substituted by one or more, especially one to three, C_1-C_7-alkyl moieties, phenyl- or naphthyl-C_1-C_7-alkylsulfinyl, sulfonyl, C_1-C_7-alkylsulfonyl, phenyl- or naphthylsulfonyl wherein phenyl or naphthyl is unsubstituted or substituted by one or more, especially one to three, C_1-C_7-alkyl moieties, phenyl- or naphthyl-C_1-C_7-alkylsulfonyl, sulfamoyl, N-mono or N,N-di-(C_1-C_7-alkyl, phenyl-, naphthyl, phenyl-C_1-C_7-alkyl or naphthyl-C_1-C_7-alkyl)-aminosulfonyl, N-mono-, N'-mono-, N,N-di- or N,N,N'-tri-(C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl and/or C_1-C_7-alkoxy-C_1-C_7-alkyl)-aminocarbonylamino and N-mono-, N'-mono-, N,N-di- or N,N,N'-tri-(C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl and/or C_1-C_7-alkoxy-C_1-C_7-alkyl) aminosulfonylamino; or is C_3-C_{10}-cycloalkyl or C_3-C_{10}-cycloalkyl-C_1-C_7-alkyl;

or a (preferably pharmaceutically acceptable) salt thereof.

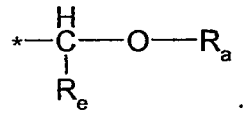
In another very preferred embodiment, the invention relates to a new compound of the formula I wherein

R^1 is phenyl-, indolyl- or quinolyl-C_1-C_7-alkanoyl (preferably –carbonyl or –acetyl) wherein the phenyl, indolyl or quinolyl is substituted by C_1-C_7-alkyloxy-C_1-C_7-alkyloxy, C_1-C_7-alkyloxy-C_1-C_7-alkyl or C_1-C_7-alkyloxy-C_1-C_7-alkyloxy-C_1-C_7-alkyland may further be substituted by one or more, e.g. up to three, C_1-C_7-alkyl (especially methyl) and/or C_1-C_7-alkyloxy moieties;

R^2 is C_1-C_7-alkyl;

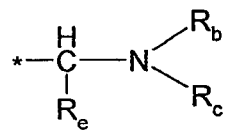
R^3 is a moiety selected from the group of moieties of the formulae

(a)

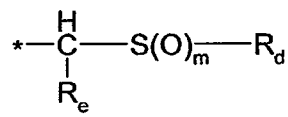


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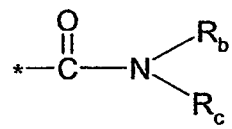
(b)



(c)



(f)



and

where in any of the moieties of the formulae given above under (a), (b), (c) and (f) the asterisk (*) shows the bond binding the respective moiety R^3 to the rest of the molecule in formula I,

wherein

R_a is hydrogen or N-mono- or N,N-di-(C_1-C_7-alkyl, (unsubstituted or halo-substituted) phenyl or naphthyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl or C_3-C_8-cycloalkyl)-aminocarbonyl;

each of R_b and R_c is, independently of the other, selected from hydrogen, C_1-C_7-alkyl, phenyl, naphthyl, naphthyl-C_1-C_7-alkyl, C_3-C_8-cycloalkylcarbonyl (= C_3-C_8-cycloalkyl-C(=O)-), , C_3-C_8cycloalkyl-C_1-C_7-alkylcarbonyl, unsubstituted or mono-, di- or tri-(halo, C_1-C_7-alkoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyl and/or C_1-C_7-alkyl)-substituted phenyl- or naphthyl-C_1-C_7-alkanoyl, preferably benzoyl or phenylacetyl, (tetrahydrofuranyl or tetrahydropyranyl)-carbonyl or (tetrahydrofuranyl or tetrahydropyranyl)-C_1-C_7-alkyl-carbonyl, such as tetrahydrofuranyl-carbonyl, tetrahydropyranylcarbonyl, tetrahydrofuranylacetyl or tetrahydropyranylacetyl, C_1-C_7-alkylsulfonyl (= C_1-C_7-alkanesulfonyl) or (unsubstituted or [C_1-C_7-alkyl-, halo-lower alkyl-, halo, C_1-C_7-alkyloxy-, cyano-, C_1-C_7-alkanoyl- and/or C_1-C_7-alkylsulfonyl-]substituted) (phenyl- or naphthyl)-C_1-C_7-alkylsulfonyl, with the proviso that if R_c is hydrogen, C_1-C_7-alkyl, phenyl, naphthyl or naphthyl-C_1-C_7-alkyl, then R_b can also be phenyl-C_1-C_7-alkyl; R_d is unsubstituted or [C_1-C_7-alkyl-, phenyl-, halo-lower alkyl-, halo, oxo-C_1-C_7-alkyl-, C_1-C_7-alkyloxy-, phenyl-C_1-C_7-alkoxy-, halo-C_1-C_7-alkyloxy-, phenoxy-, C_1-C_7-

alkanoylamino-, cyano-, C_1-C_7-alkanoyl- and/or C_1-C_7-alkylsulfonyl-]substituted (phenyl- or naphthyl)-C_1-C_7-alkyl;
R_e is hydrogen; and
m is 2;

each of R^4 and R^5 is hydrogen; and
T is carbonyl or preferably methylene;

or a (preferably pharmaceutically acceptable) salt thereof.

In the following, preferred definitions are provided individually for each variant. It should be noted that each of the preferred definitions for any variant can be combined with any preferred definition of another variant(s).

Preferred definitions for R^1

R^1 is as defined in the claims, preferably R^1 is acyl as defined herein, more preferably bearing a carbonyl group.

In a first embodiment R^1 is unsubstituted or substituted aryl-carbonyl.
Preferred examples for the aryl moiety of the acyl substituent are phenyl and naphthyl, more preferably phenyl. When the aryl moiety is substituted, it is preferably preferably mono-, di- or tri-substituted, more preferably di-substituted. Suitable substituents for the aryl moiety are as defined herein, preferably -(C_0-C_7-alkylene)-$(X)_r$-(C_1-C_7-alkylene)-$(Y)_s$-(C_0-C_7-alkylene)-H, wherein r and s are 0 or 1 and Y and X are independently O , NH or NH-CO-O-; or is halo, such as Cl or F, hydroxy, phenyl- or naphthyloxy, phenyl- or naphthyl-C_1-C_7-alkyloxy, monocyclic heterocyclyl-C_1-C_7-alkyloxy, wherein heterocyclyl is preferably a 5- or 6-membered ring containing a nitrogen atom, such as isoxazolyl; nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano, more preferably -(C_0-C_7-alkylene)-$(X)_r$-(C_1-C_7-alkylene)-$(Y)_s$-(C_0-C_7-alkylene)-H, monocyclic heterocyclyl-C_1-C_7-alkyloxy, phenyl- or naphthyl-C_1-C_7-alkyloxy or halo. When the alkylene moieties of the formula -(C_0-C_7-alkylene)-$(X)_r$-(C_1-C_7-alkylene)-$(Y)_s$-(C_0-C_7-alkylene)-H are substituted, they are preferably substituted by one or more, more preferably three halo such as F. Preferred examples of -(C_0-C_7-alkylene)-$(X)_r$-(C_1-C_7-alkylene)-$(Y)_s$-(C_0-C_7-alkylene)-H include –(O or NH, preferably O)-C_1-C_7-alkyl, -C_1-C_7-alkyl, -

(O or NH, preferably O)-C_1-C_7-alkylene-(O or NH, preferably O)-C_1-C_7-alkyl, -(O or NH, preferably O)-C_1-C_7-alkylene-(O or NH, preferably O)-H, -C_1-C_7-alkylene-(O or NH, preferably O)-C_1-C_7-alkylene-(O or NH, preferably O)-C_1-C_7-alkyl, -C_1-C_7-alkylene-(O or NH, preferably O)-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, –(O or NH, preferably O)-halo-C_1-C_7-alkyl, or -(O or NH, preferably O)-C_1-C_7-alkylene-(O or NH, preferably O)-halo-C_1-C_7-alkyl, most preferably -OMe, -OC_3H_6OMe, methyl, ethyl, t-butyl, -$CH_2OC_2H_4OMe$, -$OC_2H_4OC_2H_4$, -OC_3H_6OH, -C_4H_8OMe, -CHF_2, -OCF_3, -$OC_2H_4CF_3$, -$OC_3H_6CF_3$, and -$OC_3H_6OCF_3$. In preferred embodiments, the aryl moiety is di-substituted whereby both substituents are -(C_0-C_7-alkylene)-$(X)_r$-(C_1-C_7-alkylene)-$(Y)_s$-(C_0-C_7-alkylene)-H as defined herein, more preferably one substituent is –O-C_1-C_7-alkyl, such as OMe, or -C_1-C_7-alkyl, such as methyl or ethyl, and the other is -O-C_1-C_7-alkylene-O-C_1-C_7-alkyl, such as -OC_3H_6OMe.

In a second embodiment R^1 is unsubstituted or substituted heterocyclyl-carbonyl.
Preferred examples for the heterocyclyl moiety of the acyl substituent are mono- or bicyclic, preferably bicyclic, heterocyclyl. Preferred are aromatic ring systems, or in particular if a bicyclic moiety is contemplated, partially saturated ring systems, in particular whereby one of the rings is aromatic and the other is saturated. Most preferred are aromatic ring systems. The heterocyclyl moiety has preferably 1, 2 or 3, more preferably 1 or 2 heteroatoms selected from O, N or S, more preferably O or N. Particularly preferred examples include pyrrolyl, furanyl, thienyl (= thiophenyl), thiazolyl, pyrazolyl, triazolyl, tetrazolyl, oxetidinyl, 3-(C_1-C_7-alkyl)-oxetidinyl, pyridyl, pyrimidinyl, morpholino, thiomorpholino, piperidinyl, piperazinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrofuran-onyl, tetrahydro-pyranyl, 1H-indazolyl, benzofuranyl, benzothiophenyl, benzimidazolyl, benzopyrazolyl, benzo[1,2,5]oxadiazolyl, and 3,4-dihydro-2H-benzo[1,4]dioxinyl, or more preferably indolyl, isoquinolyl, quinolyl and 3,4-dihydro-2H-benzo[1,4] dioxinyl or especially indolyl, and 3,4-dihydro-2H-benzo[1,4] dioxinyl. When the heterocyclyl moiety is substituted, it is preferably mono- or di-substituted, most preferably di-substituted. Suitable substituents for the heterocyclyl moiety are as defined herein, preferably -(C_0-C_7-alkylene)-$(X)_r$-(C_1-C_7-alkylene)-$(Y)_s$-(C_0-C_7-alkylene)-H, wherein r and s are 0 or 1 and Y and X are independently O , NH or NH-CO-O-, halo-C_1-C_7-alkyl, halo, hydroxy, phenyl- or naphthyloxy, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano. Preferred examples of -(C_0-C_7-alkylene)-$(X)_r$-(C_1-C_7-alkylene)-$(Y)_s$-(C_0-C_7-alkylene)-H include –(O or NH, preferably O)-C_1-C_7-alkyl, -C_1-C_7-alkyl, -(O or NH, preferably O)-C_1-C_7-alkylene-(O or NH, preferably O)-C_1-C_7-alkyl, -(O or NH, preferably O)-C_1-C_7-alkylene-(O or NH, preferably O)-H, -C_1-C_7-

alkylene-(O or NH, preferably O)-C_1-C_7-alkylene-(O or NH, preferably O)-C_1-C_7-alkyl, -C_1-C_7-alkylene-(O or NH, preferably O)-C_1-C_7-alkyl, more preferably -C_1-C_7-alkyl, -O-C_1-C_7-alkylene-O-C_1-C_7-alkyl, or -C_1-C_7-alkylene-O-C_1-C_7-alkyl, still more preferably methyl, ethyl, -C_2H_4-NH-CO-OMe, -$CH_2OC_2H_4OMe$, -$OC_2H_4OC_2H_4$, -OC_3H_6OH, -C_2H_4OMe, -C_3H_6OMe and –NH-C_3H_6OMe, yet more preferably - methyl, -OC_3H_6OMe and -C_3H_6OMe. Most preferably the heterocyclyl moiety is substituted by methyl and/or -C_3H_6OMe.

Preferred definitions for R^2

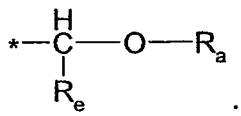
R^2 is as defined in the claims, preferably R^2 is in a first embodiment unsubstituted or substituted alkyl as defined herein. Preferred examples are branched or straight chain C_1-C_7-alkyl which may be substituted or unsubstituted. In a preferrred embodiment, R^2 is branched alkyl such as isopropyl, isobutyl, sec-butyl or tert-butyl, isopentyl, 1-ethylpropyl, and 1,2-dimethyl-propyl, most preferably isopropyl. Branched alkyl is preferably unsubstituted. If the alkyl moiety is substituted, suitable substituents are as defined herein, preferably O-C_1-C_4-alkyl, halo, hydroxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano.

Preferably in a second embodiment R^2 is cycloalkyl. Preferred examples for the cycloalkyl moiety are monocyclic rings, preferably C_3-C_7-cycloalkyl, more preferably C_3, C_4, C_5 and C_6-cycloalkyl, most preferably cyclopropyl. The cycloalkyl moiety may be substituted or unsubstituted. When the cycloalkyl moiety is substituted, it is preferably mono-substituted. Suitable substituents for the cycloalkyl moiety are as defined herein, preferably O-C_1-C_4-alkyl, halo, hydroxy, unsubstituted or substituted phenyl, naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano, most preferably phenyl or naphthyl. Most preferably, the cycloalkyl moiety is unsubstituted.

Preferred definitions for R^3

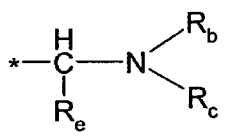
R^3 is as defined in the claims, preferably R^3 is a moiety selected from the group of moieties of the formulae

(a)

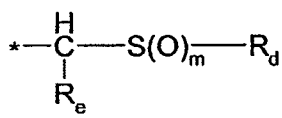


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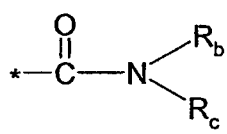
(b)



(c)



(f)



and

more preferably (a), (b) or (f), still more preferably (a) or (b), most preferably (b), where in any of the moieties of the formulae given above under (a), (b), (c) and (f) the asterisk (*) shows the bond binding the respective moiety R^3 to the rest of the molecule in formula I, wherein

R_a is acyl selected from C_1-C_7-alkanoyl, unsubstituted or mono-, di- or tri-(halo, C_1-C_7-alkoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyl and/or C_1-C_7-alkyl)-substituted) phenyl-C_1-C_7-alkanoyl, C_3-C_8-cycloalkylcarbonyl or C_3-C_8-cycloalkyl-C_1-C_7-alkyl-carbonyl, (tetrahydrofuranyl or tetrahydropyranyl)-carbonyl or (tetrahydrofuranyl or tetrahydropyranyl)-C_1-C_7-alkyl-carbonyl, N-mono- or N,N-di-(C_1-C_7-alkyl)-aminocarbonyl, N-[phenyl or phenyl-C_1-C_7-alkyl]-aminocarbonyl, N-[C_3-C_8-cycloalkyl or C_3-C_8-cycloalkyl-C_1-C_7-alkyl]-aminocarbonyl, C_1-C_7-alkylaminocarbonyl, N-(phenyl-C_1-C_7-alkyl)(C_1-C_7-alkyl)-aminocarbonyl, N-(phenyl-C_1-C_7-alkyl)(C_3-C_8-cycloalkyl-C_1-C_7-alkyl)-aminocarbonyl, N-(C_1-C_7-alkyl)(C_3-C_8-cycloalkyl-C_1-C_7-alkyl)-aminocarbonyl, N-(phenyl-C_1-C_7-alkyl)(C_3-C_8-cycloalkyl)-aminocarbonyl, N-(heterocyclyl-C_1-C_7-alkyl)(C_3-C_8-cycloalkyl)-aminocarbonyl, N-(heterocyclyl)(C_3-C_8-cycloalkyl)-aminocarbonyl; or is hydrogen;

R_b is C_1-C_7-alkyl or – in each case unsubstituted or substituted - phenyl, naphthyl, phenyl-C_1-C_7-alkyl or naphthyl-C_1-C_7-alkyl wherein in the case of a substituted moiety the substituents are one or more, especially up to three, substituents independently selected from the group

consisting of C_1-C_7-alkyl, C_2-C_7-alkenyl, C_2-C_7-alkinyl, hydroxy-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, such as trifluoromethyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, amino-C_1-C_7-alkyl, C_1-C_7-alkoxy, hydroxy-C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, C_1-C_7-alkanoyloxy, amino, mono- or di-(C_1-C_7-alkyl)-amino, C_1-C_7-alkanoylamino, C_1-C_7-alkylsulfonylamino, C_1-C_7-alkoxy-carbonyl, carboxy-C_1-C_7-alkyl, halo, hydroxy, halo-C_1-C_7-alkoxy, halo-C_1-C_7-alkylthio, nitro, carboxyl, C_1-C_7-alkyl-carbonyl, halo-C_1-C_7-alkylcarbonyl, hydroxy-C_1-C_7-alkylcarbonyl, C_1-C_7-alkoxy-C_1-C_7-alkylcarbonyl, halo-C_1-C_7-alkoxycarbonyl, carbamoyl, cyano, C_1-C_7-alkylsulfinyl, sulfonyl, C_1-C_7-alkylsulfonyl, halo-C_1-C_7-alkylsulfonyl, hydroxy-C_1-C_7-alkylsulfonyl, C_1-C_7-alkoxy-C_1-C_7-alkylsulfonyl, sulfamoyl and N-mono or N,N-di-(C_1-C_7-alkyl) -aminosulfonyl; or is acyl as just defined under R_a or selected from unsubstituted mono-, di- or tri-(halo and/or C_1-C_7-alkyl)-substituted (phenyl- or phenyl-C_1-C_7-alkyl)-sulfonyl, C_1-C_7-alkylsulfonyl;

R_c is, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkyloxy-C_1-C_7-alkyl, unsubstituted or substituted C_3-C_8-cycloalkyl-C_1-C_7-alkyl, or preferably hydrogen, unsubstituted or substituted C_3-C_8-cycloalkyl or unsubstituted or substituted C_1-C_7-alkyl;

R_d is unsubstituted or substituted phenyl- or naphthyl-C_1-C_7-alkyl wherein in the case of a substituted moiety the substituents are one or more, especially up to three, substituents independently selected from those mentioned for unsubstituted of substituted phenyl- or naphthyl-C_1-C_7-alkyl under R_b , or is -N(R_b)(R_c);

R_e is C_1-C_7-alkyl or preferably hydrogen; and

m is 2;

preferably R_a is hydrogen or N-mono- or N,N-di-(C_1-C_7-alkyl, (unsubstituted or halo-substituted) phenyl or naphthyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl C_3-C_8-cycloalkyl-C_1-C_7-alkyl, heterocyclyl-C_1-C_7-alkyl, heterocyclyl and/or C_3-C_8-cycloalkyl)-aminocarbonyl;

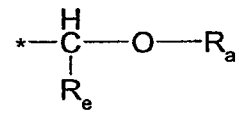
each of R_b and R_c is, independently of the other, is selected from hydrogen, C_1-C_7-alkyl, C_3-C_8-cycloalkyl-C_1-C_7-alkyl, C_3-C_8-cycloalkyl, unsubstituted or substituted aryl such as phenyl, naphthyl, naphthyl-C_1-C_7-alkyl, or acyl such as C_3-C_8-cycloalkylcarbonyl, C_3-C_8cycloalkyl-C_1-C_7-alkylcarbonyl, unsubstituted or mono-, di- or tri-(halo, C_1-C_7-alkoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyl and/or C_1-C_7-alkyl)-substituted phenyl- or naphthyl-C_1-C_7-alkanoyl, (tetrahydrofuranyl or tetrahydropyranyl)-carbonyl or (tetrahydrofuranyl or tetrahydropyranyl)-C_1-C_7-alkyl-carbonyl, C_1-C_7-alkylsulfonyl or (unsubstituted or [C_1-C_7-alkyl-, halo-lower alkyl-, halo, C_1-C_7-alkyloxy-, cyano-, C_1-C_7-alkanoyl- and/or C_1-C_7-alkylsulfonyl-]substituted) (phenyl- or naphthyl)-C_1-C_7-alkylsulfonyl, with the proviso that if R_c is hydrogen, C_1-C_7-alkyl, phenyl, naphthyl or naphthyl-C_1-C_7-alkyl, then R_b can also be phenyl-C_1-C_7-alkyl;

R_d is unsubstituted or [C_1-C_7-alkyl-, phenyl-, halo-lower alkyl-, halo, oxo-C_1-C_7-alkyl-, C_1-C_7-alkyloxy-, phenyl-C_1-C_7-alkoxy-, halo-C_1-C_7-alkyloxy-, phenoxy-, C_1-C_7-alkanoylamino-, cyano-, C_1-C_7-alkanoyl- and/or C_1-C_7-alkylsulfonyl-]substituted (phenyl- or naphthyl)-C_1-C_7-alkyl;

R_e is hydrogen; and

m is 2.

R^3 is in a first embodiment a moiety of the formula (a)



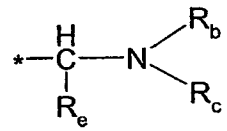
In this embodiment, R_a is as defined herein, preferably, R_a is hydrogen or acyl, preferably acyl. Acyl is preferably selected from C_1-C_7-alkanoyl, unsubstituted or mono-, di- or tri-(halo, C_1-C_7-alkoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyl and/or C_1-C_7-alkyl)-substituted) phenyl-C_1-C_7-alkanoyl, C_3-C_8-cycloalkylcarbonyl or C_3-C_8-cycloalkyl-C_1-C_7-alkyl-carbonyl, (tetrahydrofuranyl or tetrahydropyranyl)-carbonyl or (tetrahydrofuranyl or tetrahydropyranyl)-C_1-C_7-alkyl-carbonyl, and (C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or napthyl-C_1-C_7-alkyl)-oxycarbonyl, or preferably from N-mono- or N,N-di-substituted aminocarbonyl, in particular N-mono- or N,N-di-(C_1-C_7-alkyl)-aminocarbonyl, such as N,N-di-(CH_2CHCH_3)-aminocarbonyl or N-(CH_2CHCH_3)(methyl)-aminocarbonyl, N-[phenyl or phenyl-C_1-C_7-alkyl, such as phenyl–CH_2- or as phenyl–$CH(CH_2CH_3)$-]-aminocarbonyl, N-[C_3-C_8-cycloalkyl or C_3-C_8-cycloalkyl-C_1-C_7-alkyl]-aminocarbonyl, C_1-C_7-alkylaminocarbonyl, N-(phenyl-C_1-C_7-alkyl)(C_1-C_7-alkyl)-aminocarbonyl, such as N-(phenyl–CH_2-)(methyl or ethyl)aminocarbonyl, N-(phenyl-C_1-C_7-alkyl)(C_3-C_8-cycloalkyl-C_1-C_7-alkyl)-aminocarbonyl, such as N-(phenyl–CH_2-)(cyclopropyl-CH_2-)aminocarbonyl, N-(C_1-C_7-alkyl)(C_3-C_8-cycloalkyl-C_1-C_7-alkyl)-aminocarbonyl, such as N-(methyl)(cyclohexyl-CH_2-)aminocarbonyl, N-(phenyl-C_1-C_7-alkyl)(C_3-C_8-cycloalkyl)-aminocarbonyl, such as N-(phenyl–CH_2-) (cyclopropyl)-aminocarbonyl, N-(heterocyclyl-C_1-C_7-alkyl)(C_3-C_8-cycloalkyl)-aminocarbonyl, such as N-(heterocyclyl-C_1-C_7-alkyl)(cyclopropyl)-aminocarbonyl and N-(heterocyclyl)(C_3-C_8-cycloalkyl)-aminocarbonyl, such as N-(heterocyclyl)(cyclopropyl)-aminocarbonyl, whereby heterocyclyl is in each instance preferably a monocyclic, such as 5- or 6- membered monocyclic, preferaby saturated ring systems or aromatic ring systems, in particular saturated ring systems. The heterocyclyl moiety has preferably 1, 2 or 3, more preferably 1 or 2 heteroatoms selected from O, N or S, more preferably O or N. Particularly preferred examples include 5- or 6-

membered rings preferably containing an oxygen atom, in particular tetrahydropyranyl or tetrahydrofuranyl. When the heterocyclyl moiety is substituted, it is preferably mono-substituted. Suitable substituents for the heterocyclyl moiety are as defined herein, preferably halo, hydroxy, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano, more preferably phenyl-C_1-C_7-alkyl,. Suitable phenyl substituents include C_1-C_7-alkyl, -O-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, halo, hydroxyl and amino. Most preferably the heterocyclyl moiety is unsubstituted.

In this embodiment, R_e is as defined herein, preferably, R_e is hydrogen.

When R^3 is a moiety of the formula (a), then one or more, preferably all of the following substituents have the following definition:
R^1 is substituted phenyl carbonyl as defined herein, in particular whereby one substituent is –O-C_1-C_7-alkyl, such as OMe, or -C_1-C_7-alkyl, such as methyl or ethyl, and the other is -O-C_1-C_7-alkylene-O-C_1-C_7-alkyl, such as -OC_3H_6OMe; or R^1 is substituted aromatic heterocyclylcarbonyl, in particular bicyclic heterocyclylcarbonyl, such as indolyl-carbonyl, whereby the heterocyclyl moiety is substituted by methyl and/or -C_3H_6OMe;
R^2 is branched alkyl, such as isopropyl;
T is methylene, and
R^4 and R^5 are hydrogen.

R^3 is in a second embodiment a moiety of the formula (b)



In this embodiment, R_b is as defined herein, preferably R_b is selected from hydrogen, C_1-C_7-alkyl, C_3-C_8-cycloalkyl-C_1-C_7-alkyl, C_3-C_8-cycloalkyl, unsubstituted or substituted aryl such as phenyl, naphthyl, naphthyl-C_1-C_7-alkyl, or acyl, more preferably unsubstituted or substituted aryl or acyl, most preferably acyl, each as defined herein.

When R_b is unsubstituted or substituted aryl, preferred examples are phenyl or naphthyl, more preferably phenyl, which are each unsubstituted or substituted by a suitable substituent such as C_1-C_7-alkyl, -O-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, halo, hydroxy, phenyl- or naphthyloxy,

phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano; preferably each are unsubstituted.

When R_b is acyl, preferred examples are selected from the group consisting of (a) to (p), most preferably (e):

(a) Unsubstituted or substituted mono- or bicyclic aryl-carbonyl
Preferred examples of the aryl moiety include mono- or bicyclic aryl with 6 to 22 carbon atoms, whereby one of the rings of the bicyclic aryl may be a partially or fully saturated ring condensed to the other aromatic ring, especially phenyl, indanyl, indenyl, 1,2,3,4-tetrahydronaphthyl or naphthyl, more preferably phenyl, indanyl, or 1,2,3,4-tetrahydronaphthyl. When the aryl moiety is substituted, it is preferably mono- or di-substituted. In particular, phenyl is preferably unsubstituted, mono- or di-substituted, and indanyl or 1,2,3,4-tetrahydronaphthyl are preferably unsubstituted. Suitable substituents are as defined herein, preferably C_1-C_7-alkyl, -O-C_1-C_7-alkyl, such as OMe, halo-C_1-C_7-alkyl, halo, such as Cl, -O-C_1-C_7-alkylene-O-alkyl, such as O-$C_3H_6OCH_3$, hydroxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano, unsubstituted or substituted, preferably unsubstituted, heterocyclyl or unsubstituted or substituted, preferably unsubstituted, heterocyclyl-C_1-C_4-alkyl, such as heterocyclyl-CH_2, whereby the heterocyclyl moiety in each case is preferably monocyclic 5- or 6-membered heterocyclyl, preferably containing an N and/or O atom, such as tetrahydrofuranyl or tetrahydropyranyl, piperidinyl, pyrrolidinyl, piperazinyl or morpholinyl, most preferably heterocyclyl, heterocyclyl-CH_2, -O-C_1-C_7-alkyl, -O-C_1-C_7-alkylene-O-alkyl and/or halo.

(b) unsubstituted or substituted mono- or bicyclic heterocyclylcarbonyl
Preferred examples for the heterocyclyl moiety are mono- or bicyclic rings. Preferred are 3 to 14, more preferably 5 to 11 membered ring systems. The heterocyclyl moiety may be saturated, partially saturated or aromatic, in particular if a monocyclic moiety is contemplated, aromatic or saturated rings, or, in particular if a bicyclic moiety is contemplated, aromatic or partially saturated ring systems, in particular whereby one of the rings is aromatic and the other is saturated or partially saturated. The heterocyclyl moiety has preferably 1, 2 or 3, more preferably 1 or 2 heteroatoms selected from O, N or S, more

preferably O or N. Particularly preferred examples include 5- or 6-membered rings preferably containing a nitrogen or an oxygen atom, in particular pyrrolidinyl, oxazolyl, pyrrolidin-2-onyl, pyrrolyl, piperidyl, furanyl, pyrimidyl, pyridyl, pyrazinyl, isoxazolyl, pyrrolidin-2-onyl, tetrahydrofuranyl, or tetrahydropyranyl; or 9- to 11-membered bicyclic ring systems preferably containing at least one nitrogen and/or oxygen atom, in particular indolyl, 2,3-dihydro-benzo[1,4]dioxinyl, chromanyl, 2H-chromenyl, 3,4-dihydro-1H-quinolin-2-onyl, benzo[d]isoxazolyl, 4,5,6,7-tetrahydro-benzo[d]isoxazolyl, 3a,4,5,6,7,7a-hexahydro-benzo[d]isoxazolyl, 1,4,5,6,-tetrahydro-cyclopentapyrazolyl, 3,4-dihydro-2H-benzo[b][1,4]dioxepinyl, benzofuranyl, 4H-benzo[1,4]oxazin-3-onyl, benzooxazolyl, benzo[1,2,5]oxadiazolyl, benzimidazolyl or 3,4-dihydro-2H-benzo[1,4]oxazinyl, more preferably pyrazinyl, isoxazolyl, pyrrolidin-2-onyl, tetrahydrofuranyl, tetrahydropyranyl, indolyl, 2,3-dihydro-benzo[1,4]dioxinyl, chromanyl, 2H-chromenyl, 3,4-dihydro-1H-quinolin-2-onyl, benzo[d]isoxazolyl, 4,5,6,7-tetrahydro-benzo[d]isoxazolyl, 3a,4,5,6,7,7a-hexahydro-benzo[d]isoxazolyl, 1,4,5,6,-tetrahydro-cyclopentapyrazolyl, or 3,4-dihydro-2H-benzo[b][1,4]dioxepinyl. When the heterocyclyl moiety is substituted, it is preferably mono-substituted. Suitable substituents for the heterocyclyl moiety are as defined herein, preferably -C_1-C_7-alkyl, such as methyl, halo, hydroxy, C_1-C_7-alkanoyl, unsubstituted or substituted, preferably unsubstituted, phenyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyl, unsubstituted or substituted, preferably unsubstituted, C_3-C_8-cycloalkyl, such as cyclopropyl, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano, more preferably phenyl, -C_1-C_7-alkyl or C_3-C_8-cycloalkyl. Suitable phenyl and cycloalkyl substituents include C_1-C_7-alkyl, -O-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, halo, hydroxyl and amino. Most preferably the heterocyclyl moiety is unsubstituted or is mono-substituted with phenyl, -C_1-C_7-alkyl or C_3-C_8-cycloalkyl.

(c) unsubstituted or substituted mono- or bicyclic cycloalkylcarbonyl

Preferred examples for the cycloalkyl moiety are monocyclic rings, preferably C_3-C_8-cycloalkyl, more preferably C_3, C_4, C_5, C_6 and C_7-cycloalkyl. The cycloalkyl moiety may be substituted or unsubstituted. C_3, C_4, C_5, and C_7-cycloalkyl are preferably unsubstituted and C_6-cycloalkyl is preferably unsubstituted or substituted. When the cycloalkyl moiety is substituted, it is preferably mono-substituted. Suitable substituents for the cycloalkyl moiety are as defined herein, preferably O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, unsubstituted or substituted phenyl, naphthyl, unsubstituted or substituted, preferably unsubstituted,

phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, carboxyl, and cyano, most preferably O-C_1-C_4-alkyl or hydroxy.

(d) unsubstituted or substituted alkylcarbonyl

Preferred examples for the alkyl moiety are branched or straight chain C_1-C_7-alkyl which may be substituted or unsubstituted. In one embodiment, the alkyl moiety is branched alkyl such as isopropyl, isobutyl, sec-butyl or tert-butyl, isopentyl, 1-ethylpropyl, 2,2-dimethyl-propyl and 1,2-dimethyl-propyl, most preferably isobutyl, isopentyl and 2,2-dimethyl-propyl. In another embodiment the alkyl moiety is straight chain alkyl such as methyl, ethyl, n-propyl, n-butyl or n-pentyl, preferably methyl, ethyl or n-propyl. Alkyl is preferably substituted. When the alkyl moiety is substituted, it is preferably mono-, di- or tri-substituted, more preferably mono-substituted. Suitable substituents for the alkyl moiety are as defined herein, preferably O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, unsubstituted or substituted phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, aminocarbonyl, N-mono- or N,N-di-substituted aminocarbonyl, such as CONHMe, carboxyl, C_1-C_7-alkyloxycarbonyl, such as COOMe, and cyano, whereby suitable phenyl or naphthyl substituents include C_1-C_7-alkyl, such as methyl, -O-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, halo, hydroxyl and amino, preferably C_1-C_7-alkyl, and whereby suitable amino substituents include C_1-C_7-alkyl, such as methyl, phenyl or cyclopropyl, preferably C_1-C_7-alkyl. Most preferably the alkyl moiety is mono-substituted by -O-C_1-C_7-alkyl, hydroxyl, C_1-C_7-alkanoylamino, unsubstituted or di-substituted phenyloxy, aminocarbonyl, N-mono- or N,N-di-substituted aminocarbonyl and C_1-C_7-alkyloxycarbonyl.

(e) unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkylcarbonyl

Preferably aryl alkyl is aryl-C_{1-6} alkyl, more preferably aryl-C_{1-4} alkyl, in particular aryl-CH_2-, aryl-CH_2CH_2-, aryl-$CH(CH_3)$-, aryl-$CH_2CH(CH_3)$- or aryl-$C(CH_3)_2$-, most preferably aryl-CH_2-. The alkyl moiety, in particular when aryl alkyl is aryl-CH_2- or aryl-CH_2CH_2-, may be substituted, preferably mono-substituted. Examples of preferred substituents include O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, carboxyl, and cyano or unsubstituted or substituted, preferably unsubstituted, phenyl, whereby suitable phenyl substituents include C_1-C_7-alkyl, -O-C_1-C_7-

alkyl, halo-C_1-C_7-alkyl, halo, hydroxyl and amino; most preferably unsubstituted phenyl, C_1-C_7-alkanoylamino, O-C_1-C_4-alkyl or hydroxyl.

Preferred examples of the aryl moiety include mono- or bicyclic aryl with 6 to 22 carbon atoms, whereby one of the rings of the bicyclic aryl may be a partially or fully saturated ring condensed to the other aromatic ring, especially phenyl, indanyl, indenyl, 1,2,3,4-tetrahydronaphthyl or naphthyl, more preferably phenyl or naphthyl. When the aryl moiety is substituted, it is preferably mono-, di- or tri-substituted. In particular, phenyl is preferably unsubstituted, mono-, di- or tri-substituted, and naphthyl is preferably unsubstituted. In one embodiment, phenyl is preferably unsubstituted. Suitable substituents are as defined herein, preferably C_1-C_7-alkyl, -O-C_1-C_7-alkyl, such as OMe, halo-C_1-C_7-alkyl, such as CF_3, halo, such as Cl or F, -O-C_1-C_7-alkylene-O-alkyl, such as O-$C_3H_6OCH_3$, hydroxy, unsubstituted or substituted, preferably substituted, phenyl or naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, carboxyl, and cyano. Suitable substituents for the phenyl and naphthyl substituent on the aryl moiety of aryl alkylcarbonyl include C_1-C_7-alkyl, -O-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, halo, hydroxyl and amino. Most preferably the aryl alkyl moiety is unsubstituted or substituted by -O-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, substituted phenyl, C_1-C_7-alkanoylamino and/or halo.

(f) unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkylcarbonyl

Preferably heterocyclyl alkyl is heterocyclyl-C_{1-6} alkyl, more preferably heterocyclyl-C_{1-4} alkyl, in particular heterocyclyl-CH_2-, heterocyclyl-CH_2CH_2- or heterocyclyl-$CH_2C(CH_3)_2$-, most preferably heterocyclyl-CH_2-. Heterocyclyl-$CH_2C(CH_3)_2$- is particularly preferred when the heterocyclyl moiety is a 5- or 6-membered ring such as an aromatic ring, in particular pyrrolyl. Heterocyclyl-CH_2CH_2- is particularly preferred when the heterocyclyl moiety is a 5- or 6-membered ring such as an aromatic ring, in particular furanyl.

Preferred examples for the heterocyclyl moiety are mono- or bicyclic rings. Preferred are 3 to 14, more preferably 5 to 11 membered ring systems. The heterocyclyl moiety may be saturated, partially saturated or aromatic, in particular if a monocyclic moiety is contemplated, aromatic or saturated rings, or, in particular if a bicyclic moiety is contemplated, aromatic or partially saturated ring systems, in particular whereby one of the rings is aromatic and the other is saturated or partially saturated. The heterocyclyl moiety has preferably 1, 2 or 3, more preferably 1 or 2 heteroatoms selected from O, N or S, more

preferably O or N. Particularly preferred examples include 5- or 6-membered rings preferably containing a nitrogen or an oxygen atom, in particular pyrrolidinyl, oxazolyl, pyrimidyl, pyridyl, pyrazinyl, isoxazolyl, pyrrolidin-2-onyl, pyrrolyl, piperidyl, furanyl, tetrahydrofuranyl, or tetrahydropyranyl; or 9- to 11-membered bicyclic ring systems preferably containing at least one nitrogen and/or oxygen atom, in particular 4H-benzo[1,4]oxazin-3-onyl, benzooxazolyl, indolyl, 2,3-dihydro-benzo[1,4]dioxinyl, chromanyl, 2H-chromenyl, 3,4-dihydro-1H-quinolin-2-onyl, benzo[d]isoxazolyl, 4,5,6,7-tetrahydro-benzo[d]isoxazolyl, 3a,4,5,6,7,7a-hexahydro-benzo[d]isoxazolyl, 1,4,5,6,-tetrahydro-cyclopentapyrazolyl, 3,4-dihydro-2H-benzo[b][1,4]dioxepinyl, benzofuranyl, benzo[1,2,5]oxadiazolyl, benzimidazolyl or 3,4-dihydro-2H-benzo[1,4]oxazinyl, more preferably pyrrolidinyl, pyrrolidin-2-onyl, pyrrolyl, piperidyl, furanyl, tetrahydrofuranyl, tetrahydropyranyl, 4H-benzo[1,4]oxazin-3-onyl or benzooxazolyl. When the heterocyclyl moiety is substituted, it is preferably mono-substituted. Suitable substituents for the heterocyclyl moiety are as defined herein, preferably -C_1-C_7-alkyl, such as methyl, halo, hydroxy, C_1-C_7-alkanoyl, unsubstituted or substituted, preferably unsubstituted, phenyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyl, unsubstituted or substituted, preferably unsubstituted, C_3-C_8-cycloalkyl, such as cyclopropyl, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano, more preferably -C_1-C_7-alkyl or C_1-C_7-alkanoyl. Suitable phenyl and cycloalkyl substituents include C_1-C_7-alkyl, -O-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, halo, hydroxyl and amino. Most preferably the heterocyclyl moiety is unsubstituted or is mono-substituted with unsubstituted phenyl, -C_1-C_7-alkyl or C_1-C_7-alkanoyl.

(g) unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkylcarbonyl

Preferably cycloalkyl alkyl is cycloalkyl-C_{1-6} alkyl, more preferably cycloalkyl-C_{1-4} alkyl, in particular cycloalkyl-CH_2-, cycloalkyl-CH_2CH_2- or cycloalkyl-$CH_2C(CH_3)_2$-, most preferably cycloalkyl-CH_2-. The alkyl moiety may be substituted, preferably mono-substituted, including on the carbon where the cycloalkyl moiety is attached. Examples of preferred substituents include O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano, most preferably O-C_1-C_4-alkyl or hydroxyl. Preferred examples for the cycloalkyl moiety are monocyclic rings, preferably C_3-C_7-cycloalkyl, more preferably C_3, C_5 and C_6-cycloalkyl. The cycloalkyl moiety may be substituted or unsubstituted. C_3-cycloalkyl is preferably unsubstituted and C_5 and C_6-cycloalkyl are preferably unsubstituted or substituted. When the cycloalkyl moiety is substituted, it is preferably mono-substituted. Suitable

substituents for the cycloalkyl moiety are as defined herein, preferably O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, unsubstituted or substituted phenyl, naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, –NHCOEt or –$NHCOCHCH_3)_2$, carboxyl, and cyano, most preferably amino, O-C_1-C_4-alkyl or hydroxy.

(h) unsubstituted or substituted alkyloxycarbonyl

Preferred examples for the alkyl moiety are branched or straight chain C_1-C_7-alkyl which may be substituted or unsubstituted. In one embodiment, the alkyl moiety is branched alkyl such as isopropyl, isobutyl, sec-butyl or tert-butyl, isopentyl, 1-ethylpropyl, 2,2-dimethyl-propyl and 1,2-dimethyl-propyl, most preferably isobutyl, isopentyl and 2,2-dimethyl-propyl. In another embodiment the alkyl moiety is straight chain alkyl such as methyl, ethyl, n-propyl, n-butyl or n-pentyl, preferably methyl or ethyl. When the alkyl moiety is substituted, it is preferably mono-, di- or tri-substituted, more preferably mono-substituted. Suitable substituents for the alkyl moiety are as defined herein, preferably O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, unsubstituted or substituted phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, aminocarbonyl, N-mono- or N,N-di-substituted aminocarbonyl, such as CONHMe, carboxyl, C_1-C_7-alkyloxycarbonyl, such as COOMe, and cyano, whereby suitable phenyl or naphthyl substituents include C_1-C_7-alkyl, such as methyl, -O-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, halo, hydroxyl and amino, preferably C_1-C_7-alkyl, and whereby suitable amino substituents include C_1-C_7-alkyl, such as methyl, phenyl or cyclopropyl, preferably C_1-C_7-alkyl. Most preferably the alkyl moiety is mono-substituted by -O-C_1-C_7-alkyl, C_1-C_7-alkanoylamino and N-mono- or N,N-di-substituted aminocarbonyl.

(i) unsubstituted or substituted mono- or bicyclic aryl-oxycarbonyl

Preferred examples of the aryl moiety include mono- or bicyclic aryl with 6 to 22 carbon atoms, whereby one of the rings of the bicyclic aryl may be a partially or fully saturated ring condensed to the other aromatic ring, especially phenyl, indanyl, indenyl, 1,2,3,4-tetrahydronaphthyl or naphthyl, more preferably phenyl or naphthyl. When the aryl moiety is substituted, it is preferably mono- or di-substituted. In particular, phenyl is preferably unsubstituted, mono- or di-substituted, and naphthyl is preferably unsubstituted. Suitable substituents are as defined herein, preferably C_1-C_7-alkyl, -O-C_1-C_7-alkyl, such as OMe,

halo-C_1-C_7-alkyl, halo, such as Cl, -O-C_1-C_7-alkylene-O-alkyl, such as O-$C_3H_6OCH_3$, hydroxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano, unsubstituted or substituted, preferably unsubstituted, heterocyclyl or unsubstituted or substituted, preferably unsubstituted, heterocyclyl-C_1-C_4-alkyl, such as heterocyclyl-CH_2, whereby the heterocyclyl moiety in each case is preferably monocyclic 5- or 6-membered heterocyclyl, preferably containing an N and/or O atom, such as tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, pyrrolidinyl, pyrrolidin-2-onyl, piperazinyl or morpholinyl, most preferably heterocyclyl or -O-C_1-C_7-alkyl.

(j) unsubstituted or substituted mono- or bicyclic heterocyclyloxycarbonyl

Preferred examples for the heterocyclyl moiety are mono- or bicyclic rings. Preferred are 3 to 14, more preferably 5 to 11 membered ring systems. The heterocyclyl moiety may be saturated, partially saturated or aromatic, in particular if a monocyclic moiety is contemplated, aromatic or saturated, more preferably saturated, rings, or, in particular if a bicyclic moiety is contemplated, aromatic or partially saturated ring systems, in particular whereby one of the rings is aromatic and the other is saturated or partially saturated. The heterocyclyl moiety has preferably 1, 2 or 3, more preferably 1 or 2 heteroatoms selected from O, N or S, more preferably O or N. Particularly preferred examples include 5- or 6-membered rings preferably containing a nitrogen or an oxygen atom, in particular pyrrolidinyl, oxazolyl, pyrrolidin-2-onyl, pyrrolyl, piperidyl, furanyl, pyrimidyl, pyridyl, pyrazinyl, isoxazolyl, pyrrolidin-2-onyl, tetrahydrofuranyl, or tetrahydropyranyl; more preferably tetrahydrofuranyl or tetrahydropyranyl. When the heterocyclyl moiety is substituted, it is preferably mono-substituted. Suitable substituents for the heterocyclyl moiety are as defined herein, preferably -C_1-C_7-alkyl, such as methyl, halo, hydroxy, C_1-C_7-alkanoyl, unsubstituted or substituted, preferably unsubstituted, phenyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyl, unsubstituted or substituted, preferably unsubstituted, C_3-C_8-cycloalkyl, such as cyclopropyl, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano, more preferably phenyl, -C_1-C_7-alkyl or C_3-C_8-cycloalkyl. Suitable phenyl and cycloalkyl substituents include C_1-C_7-alkyl, -O-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, halo, hydroxyl and amino. Most preferably the heterocyclyl moiety is unsubstituted.

(k) unsubstituted or substituted mono- or bicyclic cycloalkyloxycarbonyl

Preferred examples for the cycloalkyl moiety are monocyclic rings, preferably C_3-C_8-cycloalkyl, more preferably C_3, C_4, C_5, C_6 and C_7-cycloalkyl, most preferably C_6-cycloalkyl. The cycloalkyl moiety may be substituted or unsubstituted, preferably unsubstituted. When the cycloalkyl moiety is substituted, it is preferably mono-substituted. Suitable substituents for the cycloalkyl moiety are as defined herein, preferably O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, unsubstituted or substituted phenyl, naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, carboxyl, and cyano, most preferably O-C_1-C_4-alkyl or hydroxy.

(l) unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyloxycarbonyl

Preferably aryl alkyl is aryl-C_{1-6} alkyl, more preferably aryl-C_{1-4} alkyl, in particular aryl-CH_2-, aryl-CH_2CH_2-, aryl-$CH(CH_3)$-, aryl-$CH_2CH(CH_3)$- or aryl-$CH(CH_2CH_3)$-, most preferably aryl-CH_2-. Preferred examples of the aryl moiety include mono- or bicyclic aryl with 6 to 22 carbon atoms, whereby one of the rings of the bicyclic aryl may be a partially or fully saturated ring condensed to the other aromatic ring, especially phenyl, indanyl, indenyl, 1,2,3,4-tetrahydronaphthyl or naphthyl, more preferably phenyl. When the aryl moiety is substituted, it is preferably mono-, di- or tri-substituted. In one embodiment, phenyl is preferably unsubstituted. Suitable substituents are as defined herein, preferably C_1-C_7-alkyl, -O-C_1-C_7-alkyl, such as OMe, halo-C_1-C_7-alkyl, such as CF_3, halo, such as Cl or F, -O-C_1-C_7-alkylene-O-alkyl, such as O-$C_3H_6OCH_3$, hydroxy, unsubstituted or substituted, preferably substituted, phenyl or naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, carboxyl, and cyano. Suitable substituents for the phenyl and naphthyl substituent on the aryl moiety of aryl alkylcarbonyl include C_1-C_7-alkyl, -O-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, halo, hydroxyl and amino.

(m) unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkyloxycarbonyl

Preferably heterocyclyl alkyl is heterocyclyl-C_{1-6} alkyl, more preferably heterocyclyl-C_{1-4} alkyl, in particular heterocyclyl-CH_2-, heterocyclyl-CH_2CH_2- or heterocyclyl-$CH_2CH(CH_3)$-, most preferably heterocyclyl-CH_2-. Heterocyclyl-$CH_2CH(CH_3)$- is particularly preferred when the heterocyclyl moiety is a 5- or 6-membered ring such as a saturated ring, in particular 1,3-dioxane. Preferred examples for the heterocyclyl moiety are mono- or bicyclic rings.

Preferred are 3 to 14, more preferably 5 to 11 membered ring systems. The heterocyclyl moiety may be saturated, partially saturated or aromatic, in particular if a monocyclic moiety is contemplated, aromatic or saturated rings, or, in particular if a bicyclic moiety is contemplated, aromatic or partially saturated ring systems, in particular whereby one of the rings is aromatic and the other is saturated or partially saturated. The heterocyclyl moiety has preferably 1, 2 or 3, more preferably 1 or 2 heteroatoms selected from O, N or S, more preferably O or N. Particularly preferred examples include 5- or 6-membered rings preferably containing a nitrogen or an oxygen atom, in particular pyrrolidinyl, oxazolyl, pyrimidyl, pyridyl, pyrazinyl, isoxazolyl, pyrrolidin-2-onyl, pyrrolyl, piperidyl, furanyl, 1,3-dioxane, tetrahydrofuranyl, or tetrahydropyranyl; more preferably pyridyl, piperidyl, isoxazolyl, tetrahydrofuranyl, tetrahydropyranyl or 1,3-dioxane. When the heterocyclyl moiety is substituted, it is preferably mono-substituted. Suitable substituents for the heterocyclyl moiety are as defined herein, preferably -C_1-C_7-alkyl, such as methyl, halo, hydroxy, C_1-C_7-alkanoyl, such as COMe, unsubstituted or substituted, preferably unsubstituted, phenyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyl, unsubstituted or substituted, preferably unsubstituted, C_3-C_8-cycloalkyl, such as cyclopropyl, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano, more preferably -C_1-C_7-alkyl or C_1-C_7-alkanoyl. Suitable phenyl and cycloalkyl substituents include C_1-C_7-alkyl, -O-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, halo, hydroxyl and amino. Most preferably the heterocyclyl moiety is unsubstituted or is mono-substituted with -C_1-C_7-alkyl or C_1-C_7-alkanoyl.

(n) unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkyloxycarbonyl

Preferably cycloalkyl alkyl is cycloalkyl-C_{1-6} alkyl, more preferably cycloalkyl-C_{1-4} alkyl, in particular cycloalkyl-CH_2-, cycloalkyl-CH_2CH_2- or cycloalkyl-$CH_2CH(CH_3)$-, most preferably cycloalkyl-CH_2-. Preferred examples for the cycloalkyl moiety are monocyclic rings, preferably C_3-C_7-cycloalkyl, more preferably C_3 and C_5 -cycloalkyl. The cycloalkyl moiety may be substituted or unsubstituted. C_3-cycloalkyl is preferably unsubstituted and C_5-cycloalkyl are preferably unsubstituted or substituted. When the cycloalkyl moiety is substituted, it is preferably mono-substituted. Suitable substituents for the cycloalkyl moiety are as defined herein, preferably O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, unsubstituted or substituted phenyl, naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-

C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, –NHCOEt or –$NHCOCHCH_3)_2$, carboxyl, and cyano, most preferably C_1-C_7-alkanoylamino.

(o) N-mono- or N,N-di-(unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkyl and/or unsubstituted or substituted alkyl)-aminocarbonyl

Preferred examples for the alkyl moiety of the unsubstituted or substituted alkyl aminocarbonyl are branched or straight chain C_1-C_7-alkyl which may be substituted or unsubstituted. In one embodiment, the alkyl moiety is branched alkyl such as isopropyl, isobutyl, sec-butyl or tert-butyl, isopentyl, 1-ethylpropyl, 2,2-dimethyl-propyl and 1,2-dimethyl-propyl, most preferably isopropyl or isobutyl. In another embodiment the alkyl moiety is straight chain alkyl such as methyl, ethyl, n-propyl, n-butyl or n-pentyl, preferably methyl or ethyl. When the alkyl moiety is substituted, it is preferably mono-, di- or tri-substituted, more preferably mono-substituted. Suitable substituents for the alkyl moiety are as defined herein, preferably O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, aminocarbonyl, N-mono- or N,N-di-substituted aminocarbonyl, such as CONHMe, carboxyl, C_1-C_7-alkyloxycarbonyl, such as COOMe, and cyano. Most preferably the alkyl moiety is unsubstituted.

Preferred examples of the aryl moiety of the unsubstituted or substituted aryl aminocarbonyl include mono- or bicyclic aryl with 6 to 22 carbon atoms, whereby one of the rings of the bicyclic aryl may be a partially or fully saturated ring condensed to the other aromatic ring, especially phenyl, indanyl, indenyl, 1,2,3,4-tetrahydronaphthyl or naphthyl, more preferably phenyl or naphthyl. When the aryl moiety is substituted, it is preferably mono- or di-substituted. Suitable substituents are as defined herein, preferably C_1-C_7-alkyl, -O-C_1-C_7-alkyl, such as OMe, halo-C_1-C_7-alkyl, halo, such as Cl, -O-C_1-C_7-alkylene-O-alkyl, such as O-$C_3H_6OCH_3$, hydroxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-

C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano. Most preferably aryl is unsubstituted.

Preferred examples for the cycloalkyl moiety moiety of the unsubstituted or substituted cycloalkyl aminocarbonyl are monocyclic rings, preferably C_3-C_8-cycloalkyl, more preferably C_3, C_4, C_5, C_6 and C_7-cycloalkyl, most preferably C_3 or C_6-cycloalkyl. The cycloalkyl moiety may be substituted or unsubstituted, preferably unsubstituted. When the cycloalkyl moiety is substituted, it is preferably mono-substituted. Suitable substituents for the cycloalkyl moiety are as defined herein, preferably O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, unsubstituted or substituted phenyl, naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, carboxyl, and cyano, most preferably O-C_1-C_4-alkyl or hydroxy.

Preferably the aryl alkyl moiety of the unsubstituted or substituted aryl alkyl aminocarbonyl is aryl-C_{1-6} alkyl, more preferably aryl-C_{1-4} alkyl, in particular aryl-CH_2-, aryl-CH_2CH_2-, or aryl-$CH(CH_2CH_3)$-, most preferably aryl-CH_2-. The alkyl moiety, in particular when aryl alkyl is aryl-CH_2-, may be substituted, preferably mono-substituted. Examples of preferred substituents include O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, carboxyl, and cyano or unsubstituted or substituted, preferably unsubstituted, phenyl, whereby suitable phenyl substituents include C_1-C_7-alkyl, -O-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, halo, hydroxyl and amino; most preferred is unsubstituted phenyl. Preferred examples of the aryl moiety include mono- or bicyclic aryl with 6 to 22 carbon atoms, whereby one of the rings of the bicyclic aryl may be a partially or fully saturated ring condensed to the other aromatic ring, especially phenyl, indanyl, indenyl, 1,2,3,4-tetrahydronaphthyl or naphthyl, more preferably phenyl. When the aryl moiety is substituted, it is preferably mono-, di- or tri-substituted. In one embodiment, phenyl is preferably unsubstituted. Suitable substituents are as defined herein, preferably C_1-C_7-alkyl, -O-C_1-C_7-alkyl, such as OMe, halo-C_1-C_7-alkyl, such as CF_3, halo, such as Cl or F, -O-C_1-C_7-alkylene-O-alkyl, such as O-$C_3H_6OCH_3$, hydroxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, carboxyl, and cyano, more preferably -O-C_1-C_7-alkyl or halo.

Preferably the heterocyclyl alkyl moiety of the unsubstituted or substituted heterocyclyl alkyl aminocarbonyl is heterocyclyl-C_{1-6} alkyl, more preferably heterocyclyl-C_{1-4} alkyl, in particular heterocyclyl-CH_2- or heterocyclyl-CH_2CH_2-, most preferably heterocyclyl-CH_2-. Preferred examples for the heterocyclyl moiety are mono- or bicyclic rings. Preferred are 3 to 14, more preferably 5 to 11 membered ring systems. The heterocyclyl moiety may be saturated, partially saturated or aromatic, in particular if a monocyclic moiety is contemplated, aromatic or saturated rings, or, in particular if a bicyclic moiety is contemplated, aromatic or partially saturated ring systems, in particular whereby one of the rings is aromatic and the other is saturated or partially saturated. The heterocyclyl moiety has preferably 1, 2 or 3, more preferably 1 or 2 heteroatoms selected from O, N or S, more preferably O or N. Particularly preferred examples include 5- or 6-membered rings preferably containing a nitrogen or an oxygen atom, in particular pyrrolidinyl, oxazolyl, pyrimidyl, pyridyl, pyrazinyl, isoxazolyl, pyrrolidin-2-onyl, pyrrolyl, piperidyl, furanyl, 1,3-dioxane, tetrahydrofuranyl, or tetrahydropyranyl; more preferably furanyl or tetrahydropyranyl. When the heterocyclyl moiety is substituted, it is preferably mono-substituted. Suitable substituents for the heterocyclyl moiety are as defined herein, preferably -C_1-C_7-alkyl, such as methyl, halo, hydroxy, C_1-C_7-alkanoyl, such as COMe, unsubstituted or substituted, preferably unsubstituted, phenyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyl, unsubstituted or substituted, preferably unsubstituted, C_3-C_8-cycloalkyl, such as cyclopropyl, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano, more preferably -C_1-C_7-alkyl or C_1-C_7-alkanoyl. Suitable phenyl and cycloalkyl substituents include C_1-C_7-alkyl, -O-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, halo, hydroxyl and amino. Most preferably the heterocyclyl moiety is unsubstituted.

Preferably the cycloalkyl alkyl moiety of the unsubstituted or substituted cycloalkyl alkyl aminocarbonyl is cycloalkyl-C_{1-6} alkyl, more preferably cycloalkyl-C_{1-4} alkyl, in particular cycloalkyl-CH_2-. Preferred examples for the cycloalkyl moiety are monocyclic rings, preferably C_3-C_7-cycloalkyl, more preferably C_6 -cycloalkyl. The cycloalkyl moiety may be substituted or unsubstituted, preferably unsubstituted. When the cycloalkyl moiety is substituted, it is preferably mono-substituted. Suitable substituents for the cycloalkyl moiety are as defined herein, preferably O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, unsubstituted or substituted phenyl, naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or

naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, –NHCOEt or –$NHCOCHCH_3)_2$, carboxyl, and cyano, most preferably C_1-C_7-alkanoylamino.

Preferred examples of N-mono- or N,N-di-(unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkyl and/or unsubstituted or substituted alkyl)-aminocarbonyl include
(unsubstituted or substituted mono- or bicyclic aryl)(unsubstituted or substituted alkyl)aminocarbonyl,
unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkyl-aminocarbonyl,
unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl-aminocarbonyl,
unsubstituted or substituted mono- or bicyclic aryl-aminocarbonyl,
unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkyl-aminocarbonyl,
di-(unsubstituted or substituted mono- or bicyclic aryl)-aminocarbonyl,
di-(unsubstituted or substituted alkyl)-aminocarbonyl,
(unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl)(unsubstituted or substituted alkyl)-aminocarbonyl,
(unsubstituted or substituted mono- or bicyclic cycloalkyl)(unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl)-aminocarbonyl,
(unsubstituted or substituted mono- or bicyclic cycloalkyl)(unsubstituted or substituted mono- or bicyclic aryl)-aminocarbonyl, and
unsubstituted or substituted mono- or bicyclic cycloalkyl-aminocarbonyl.

(p) unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkylsulfonyl
preferably aryl alkyl is aryl-C_{1-6} alkyl, more preferably aryl-C_{1-4} alkyl, in particular aryl-CH_2-, aryl-CH_2CH_2-, aryl-$CH(CH_3)$-, aryl-$CH_2CH(CH_3)$- or aryl-$CH(CH_2CH_3)$-, most preferably aryl-CH_2-. Preferred examples of the aryl moiety include mono- or bicyclic aryl with 6 to 22 carbon atoms, whereby one of the rings of the bicyclic aryl may be a partially or fully saturated ring condensed to the other aromatic ring, especially phenyl, indanyl, indenyl, 1,2,3,4-tetrahydronaphthyl or naphthyl, more preferably phenyl. When the aryl moiety is substituted, it is preferably mono-, di- or tri-substituted. In one embodiment, phenyl is preferably unsubstituted. Suitable substituents are as defined herein, preferably C_1-C_7-alkyl,

-O-C_1-C_7-alkyl, such as OMe, halo-C_1-C_7-alkyl, such as CF_3, halo, such as Cl or F, -O-C_1-C_7-alkylene-O-alkyl, such as O-$C_3H_6OCH_3$, hydroxy, unsubstituted or substituted, preferably substituted, phenyl or naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, carboxyl, and cyano. Suitable substituents for the phenyl and naphthyl substituent on the aryl moiety of aryl alkylcarbonyl include C_1-C_7-alkyl, -O-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, halo, hydroxyl and amino.

When R_b is acyl, R_c is as defined herein, preferably, R_c is hydroxy-C_1-C_7-alkyl, C_1-C_7-alkyloxy-C_1-C_7-alkyl, unsubstituted or substituted C_3-C_8-cycloalkyl-C_1-C_7-alkyl, or preferably hydrogen, unsubstituted or substituted C_3-C_8-cycloalkyl or unsubstituted or substituted C_1-C_7-alkyl, most preferably cyclopropyl or methyl. In particular, when R_b is acyl as defined under (h) to (n), R_c is preferably hydrogen, unsubstituted or substituted C_3-C_8-cycloalkyl or unsubstituted or substituted C_1-C_7-alkyl, most preferably cyclopropyl or methyl. In particular, when R_b is acyl as defined under (o), R_c is preferably unsubstituted or substituted C_3-C_8-cycloalkyl most preferably cyclopropyl. In particular, when R_b is acyl as defined under (p), R_c is preferably unsubstituted or substituted C_3-C_8-cycloalkyl most preferably methyl or isobutyl.

When R_c is hydrogen, then one or more, preferably all of the following substituents have the following definition:
R_b is unsubstituted or substituted aryl as defined herein, preferably unsubstituted phenyl, unsubstituted or substituted aryl alkylcarbonyl as defined herein, preferably unsubstituted phenyl-$C(CH_3)_2$-CO or unsubstituted phenyl-CH(OMe)-CO, unsubstituted or substituted aryl carbonyl as defined herein, preferably unsubstituted indanyl-CO-, unsubstituted or substituted heterocyclyl carbonyl as defined herein, preferably unsubstituted 2,3-dihydro-benzo[1,4]dioxinyl-CO-, unsubstituted or substituted heterocyclyl alkyl carbonyl as defined herein, preferably unsubstituted tetrahydropyranyl-CH_2-CO-
R^1 is substituted phenyl carbonyl as defined herein, in particular whereby one substituent is –O-C_1-C_7-alkyl, such as OMe, or -C_1-C_7-alkyl, such as methyl or ethyl, and the other is -O-C_1-C_7-alkylene-O-C_1-C_7-alkyl, such as -OC_3H_6OMe;
R^2 is branched alkyl, such as isopropyl;
T is methylene, and
R^4 and R^5 are hydrogen.

When R_c is unsubstituted or substituted C_1-C_7-alkyl, preferred examples are branched or straight chain C_1-C_7-alkyl which may be substituted or unsubstituted. In a preferred embodiment, R_c is branched alkyl such as isopropyl, isobutyl, sec-butyl or tert-butyl, isopentyl, 1-ethylpropyl, and 1,2-dimethyl-propyl, most preferably isopropyl. In another preferred embodiment, R_c is straight chain alkyl such as methyl, ethyl, n-propyl, n-butyl or n-pentyl, more preferably methyl or ethyl, most preferably ethyl If the alkyl moiety is substituted, suitable substituents are as defined herein, preferably O-C_1-C_4-alkyl, halo, hydroxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano. Most preferably, the alkyl moiety is unsubstituted.

When R_c is unsubstituted or substituted C_3-C_8-cycloalkyl, preferred examples for the cycloalkyl moiety are monocyclic rings, preferably C_3-C_7-cycloalkyl, more preferably C_3, C_4, C_5 and C_6-cycloalkyl, more preferably cyclopropyl or cyclobutyl, most preferably cyclopropyl. The cycloalkyl moiety may be substituted or unsubstituted. When the cycloalkyl moiety is substituted, it is preferably mono-substituted. Suitable substituents for the cycloalkyl moiety are as defined herein, preferably O-C_1-C_4-alkyl, halo, hydroxy, unsubstituted or substituted phenyl, naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano, most preferably phenyl or naphthyl. Most preferably, the cycloalkyl moiety is unsubstituted.

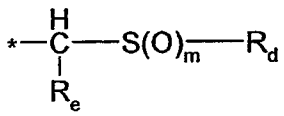
When R_c is unsubstituted or substituted C_3-C_8-cycloalkyl-C_1-C_7-alkyl, such as C_3-C_8-cycloalkyl-C_1-C_4-alkyl, in particular C_3-C_8-cycloalkyl-CH_2, preferred examples for the cycloalkyl moiety are monocyclic rings, preferably C_3-C_7-cycloalkyl, more preferably C_3, C_4, C_5 and C_6-cycloalkyl, most preferably cyclopropyl. The cycloalkyl moiety may be substituted or unsubstituted. When the cycloalkyl moiety is substituted, it is preferably mono-substituted. Suitable substituents for the cycloalkyl moiety are as defined herein, preferably O-C_1-C_4-alkyl, halo, hydroxy, unsubstituted or substituted phenyl, naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl,

carboxyl, and cyano, most preferably phenyl or naphthyl. Most preferably, the cycloalkyl moiety is unsubstituted.

When R_c is unsubstituted or substituted C_3-C_8-cycloalkyl-C_1-C_7-alkyl, then one or more, preferably all of the following substituents have the following definition:
R^1 is substituted phenyl carbonyl as defined herein, in particular whereby one substituent is -O-C_1-C_7-alkyl, such as OMe, or -C_1-C_7-alkyl, such as methyl or ethyl, and the other is -O-C_1-C_7-alkylene-O-C_1-C_7-alkyl, such as -OC_3H_6OMe;
R^2 is branched alkyl, such as isopropyl;
T is methylene, and
R^4 and R^5 are hydrogen.

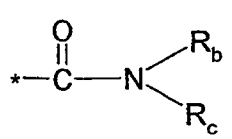
When R^3 is a moiety of formula (b), R_e is as defined herein, preferably, R_e is hydrogen.

R^3 is in a third embodiment a moiety of the formula (c)



In this embodiment, R_d is as defined herein, in particular R_d is unsubstituted or substituted phenyl- or naphthyl-C_1-C_7-alkyl wherein in the case of a substituted moiety the substituents are one or more, especially up to three, substituents independently selected from those mentioned for unsubstituted of substituted phenyl- or naphthyl-C_1-C_7-alkyl under R_b , or is -$N(R_b)(R_c)$ wherein R_b and R_c are as defined for the second embodiment above, preferably is unsubstituted or [C_1-C_7-alkyl-, phenyl-, halo-lower alkyl-, halo, oxo-C_1-C_7-alkyl-, C_1-C_7-alkyloxy-, phenyl-C_1-C_7-alkoxy-, halo-C_1-C_7-alkyloxy-, phenoxy-, C_1-C_7-alkanoylamino-, cyano-, C_1-C_7-alkanoyl- and/or C_1-C_7-alkylsulfonyl-]substituted (phenyl- or naphthyl)-C_1-C_7-alkyl; most preferably benzyl.

R^3 is in a fourth embodiment a moiety of the formula (f)



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In this embodiment, R_b is as defined herein, in particular as described with respect to the second embodiment where R^3 is a moiety of the formula (b). Preferably, R_b is aryl-alkyl, such as phenyl-C_1-C_4-alkyl, whereby the aryl moiety is unsubstituted or substituted by a suitable substituent such as C_1-C_7-alkyl, -O-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, halo, hydroxy, phenyl- or naphthyloxy, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano; preferably the aryl moiety is unsubstituted. Or R_b is unsubstituted or substituted alkyl. Preferred examples are branched or straight chain C_1-C_7-alkyl which may be substituted or unsubstituted, preferably straight chain alkyl such as methyl, ethyl, n-propyl, n-butyl or n-pentyl, preferably methyl, whereby the alkyl moiety is unsubstituted or substituted by a suitable substituent such as O-C_1-C_4-alkyl, halo, hydroxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano; preferably the alkyl moiety is unsubstituted.

In this embodiment, R_c is as defined herein, preferably, R_c is hydrogen.

When R^3 is a moiety of the formula (f), then one or more, preferably all of the following substituents have the following definition:
R^1 is substituted phenyl carbonyl as defined herein, in particular whereby one substituent is –O-C_1-C_7-alkyl, such as OMe, or -C_1-C_7-alkyl, such as methyl or ethyl, and the other is -O-C_1-C_7-alkylene-O-C_1-C_7-alkyl, such as -OC_3H_6OMe;
R^2 is branched alkyl, such as isopropyl;
T is methylene, and
R^4 and R^5 are hydrogen.

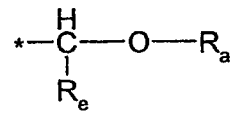
Particular embodiments of the invention, especially of compounds of the formula I and/or salts thereof, are provided in the Examples – the invention thus, in a very preferred embodiment, relates to a compound of the formula I, or a salt thereof, selected from the compounds given in the Examples, as well as the use thereof.

Process of Manufacture

A compound of formula I, or a salt thereof, is prepared analogously to methods that, for other compounds, are in principle known in the art, so that for the novel compounds of the formula I the process is novel at least as analogy process, especially as described or in ana-

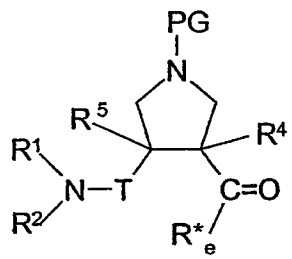
logy to methods described herein in the illustrative Examples, or modifications thereof, preferably in general by

(A) for the synthesis of a compound of the formula I wherein R^3 is a moiety of the formula (a)



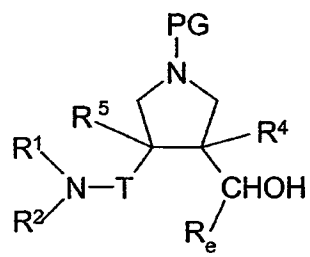
(a)

wherein R_a and R_e are as defined for a compound of the formula I and R^1, R^2, R^4, R^5 and T are as defined for a compound of the formula I, reducing a compound of the formula II,



(II)

wherein R^1, R^2, R^4, R^5 and T are as just defined, R^*_e is hydroxy or R_e as defined for a compound of the formula I and PG is a protecting group, to the corresponding hydroxy compound of the formula III,



(III)

wherein R_e is as defined for a compound of the formula I and the other moieties are as defined, which is then either deprotected to a corresponding compound of the formula I wherein R_a in the moiety of the formula (a) is hydrogen or further reacted either

(i) with a compound of the formula IV,

$$R_a^*\text{-}X \qquad \text{(IV)}$$

wherein R_a^* is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or acyl and X is a leaving group, or

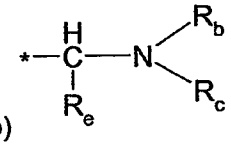
(ii) in order to introduce a moiety R_a which is N-(unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkyl or unsubstituted or substituted alkyl)-aminocarbonyl, with an isocyanato compound of the formula IV*,

$$R_a^{**}\text{-}N{=}C{=}O \qquad (IV^*)$$

wherein R_a^{**} is unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkyl or unsubstituted or substituted alkyl,

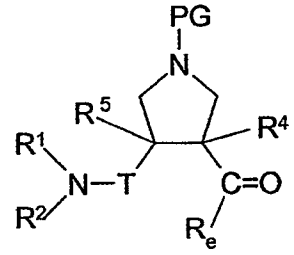
where reaction (i) or (ii) is followed by removal of any protecting group(s) to give a corresponding compound of the formula I if no further conversion requiring the presence of protecting groups is desired; or

(B) for the synthesis of a compound of the formula I wherein R^3 is a moiety of the formula (b)



(b)

wherein R_e, R_b and R_c are as defined for a compound of the formula I, and wherein R^1, R^2, R^4, R^5 and T are as defined for a compound of the formula I, reacting an aldehyde compound of the formula V,



(V)

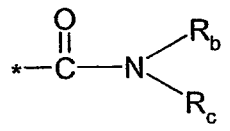
wherein R_e, R^1, R^2, R^4, R^5 and T are as defined for a compound of the formula I and PG is a protecting group,

under conditions of reductive amination with a compound of the formula VI,

$$R_b\text{-}NH\text{-}R_c \qquad (VI)$$

wherein R_b and R_c are as defined for a compound of the formula I, followed, if no further conversion requiring protecting groups is intended, by removal of any protecting group(s); or

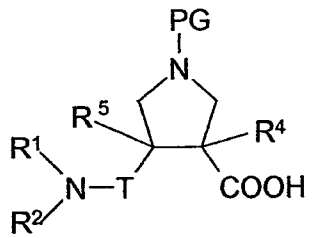
(C) for the synthesis of a compound of the formula I wherein R^3 is a moiety of the formula (f)



(f)

wherein R_b and R_c as well as R^1, R^2, R^4, R^5 and T are as defined for a compound of the formula I,

condensing an acid of the formula IIB,



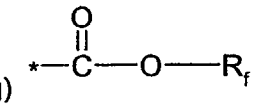
(IIB)

wherein R^1, R^2, R^4, R^5 and T are as defined for a compound of the formula I and PG is a protecting group, or a reactive derivative thereof, with an amine of the formula VI,

$$R_b\text{-NH-}R_c \qquad \text{(VI)}$$

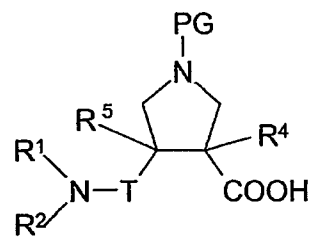
wherein R_b and R_c are as defined for a compound of the formula I, followed, if no further conversion requiring protecting groups is intended, by removal of any protecting group(s); or

(D) for the synthesis of a compound of the formula I wherein R^3 is a moiety of the formula (g)



(g)

wherein R_f is as defined for a compound of the formula I and wherein R^1, R^2, R^4, R^5 and T are as defined for a compound of the formula I, reacting an acid of the formula IIB,



(IIB)

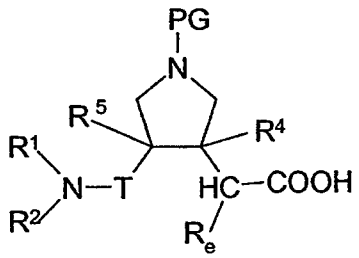
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wherein R^1, R^2, R^4, R^5 and T are as defined for a compound of the formula I and PG is a protecting group, or a reactive derivative thereof, with an alcohol or alcohol derivative of the formula VII,

$$R_f\text{-}X \qquad \text{(VII)}$$

wherein R_f is as defined for a compound of the formula I and X is hydroxy or a leaving group, followed, if no further conversion requiring protecting groups is intended, by removal of any protecting group(s); or

(E) for the synthesis of a compound of the formula I wherein R^3 is a moiety of the formula (d) or (e) as defined for a compound of the formula I and R^1, R^2, R^4 R^5 and T are as defined for a compound of the formula I, reacting a compound of the formula IIA,



(IIA)

wherein R^1, R^2, R^4, R^5, T and R_e are as defined for a compound of the formula I,
(i) for the synthesis of a compound of the formula I wherein R^3 is a moiety of the formula (d) with a compound of the formula VI,

$$R_b\text{-}NH\text{-}R_c \qquad \text{(VI)}$$

wherein R_a and R_b are as defined for a compound of the formula I, or
(ii) for the synthesis of a compound of the formula I wherein $R^3$is a moiety of the formula (e) with a compound of the formula VII,

$$R_f\text{-}X \qquad \text{(VII)};$$

wherein R_f is as defined for a compound of the formula I and X is hydroxy or a leaving group;

and, if desired, subsequent to any one or more of the processes (A), (B), (C),r (D) or (E) mentioned above, converting an obtainable compound of the formula I or a protected form thereof into a different compound of the formula I, converting a salt of an obtainable compound of formula I into the free compound or a different salt, converting an obtainable free compound of formula I into a salt thereof, and/or separating an obtainable mixture of isomers of a compound of formula I into individual isomers;

where in any of the starting materials (especially of the formulae II, IIA, IIB, III, IV, IV*, V, VI and VII), in addition to specific protecting groups mentioned, further protecting groups may be present, and any protecting groups are removed at an appropriate stage in order to obtain a corresponding compound of the formula I, or a salt thereof.

Preferred Reaction Conditions

The preferred reaction conditions for the reactions mentioned above, as well as for the transformations and conversions, are as follows (or analogous to methods used in the Examples or as described there):

The reduction under (A) preferably takes place under customary conditions for the reduction of carbonic acids to the corresponding alcohols, preferably in the presence of an appropriate complex hydride, such as borane-dimethylsulfide-complex, in an appropriate solvent, e.g. an ether, such as tetrahydrofurane, at preferred temperatures e.g. from –40 to 30 °C, e.g. from – 15 to 0 °C, or e.g. with disiamylborane or $LiAlH[OC(CH_3]_3$ in tetrahydrofurane or diethylether, sodium borohydride in ethanol or sodium borohydride in the presence of LiCl in diglycol, or the like, at preferred temperatures in the range from 0 °C to the reflux temperature of the reaction mixture.

The subsequent removal of a protecting group, e.g. PG, such as tert-butoxycarbonyl, methoxymethyl, benzyl, 2-(trimethylsilyl)-ethoxycarbonyl or tert-butyldimethylsilyl, if required, takes place under standard conditions, see also the literature mentioned below under General Process Conditions. For example, tert-butoxycarbonyl is removed in the presence of an acid, e.g. a hydrohalic acid, such as HCl, in an appropriate solvent, e.g. an ether, such as dioxane, or an alcohol, e.g. isopropanol, at customary temperatures, e.g. at room temperature, the removal of benzyl by treatment with hydrogen in the presence of a noble metal catalyst, such as palladium on charcoal, under customary reaction conditions, e.g. in an appropriate solvent, such as methanol or ethanol, and at customary temperatures, e.g. from 0 to 50 °C, the removal of 2-(trimethylsilyl)-ethoxycarbonyl can be achieved, for example, by reaction with a tetra-lower alkylammonium fluoride, such as tetraethylammoniumfluoride, in an appropriate solvent or solvent mixture, e.g. a halogenated hydrocarbon, such as methylene chloride, and/or a nitrile, such as acetonitrile, preferably at elevated temperatures, e.g. under reflux conditions, and the removal of tert-butyldimethylsilyl

in the presence of tetra-butyl ammonium fluoride, e.g. in the presence of a solvent such as tetrahydrofurane at preferred temperatures from 0 to 50 °C, e.g. at about room temperature.

The further reaction under (A) (i) (preferably with a still protected compound of the formula III) with a compound of the formula IV then preferably takes place under customary conditions for substitution reaction, e.g. in an appropriate solvent, such as an ether, e.g. tetrahydrofurane, or a halogenated hydrocarbon, e.g. methylene chloride, at appropriate temperatures, e.g. in the range from –40 °C to the reflux temperature, if useful or required in the presence of a base, such as potassium carbonate. The leaving group X is preferably halo, especially chloro, bromo or iodo, alkanesulfonyloxy, such as methanesulfonyloxy, or arylsulfonyloxy, such as p-toluolsulfonyloxy.

The further reaction under (A) (ii) (preferably with a still protected compound of the formula III) with a compound of the formula IV*, alternatively, then preferably takes place under customary conditions for the reaction of hydroxy compounds with isocyanates, for example, the reaction preferably takes place in the presence of a Lewis Acid, such as aluminium chloride, in an appropriate solvent, such as diethylether, at preferred temperatures e.g. from 0 to 50 °C. Where required, subsequent removal of protecting groups takes place as described above or below, especially as described under the general process conditions.

The reductive amination under (B) preferably takes place place under customary conditions for reductive amination, e.g. in the presence of an appropriate reducing (e.g. hydrogenation) agent, such as hydrogen in the presence of a catalyst or a complex hydride, e.g. sodium triacetoxyborohydride or sodium cyanoborohydride, in an appropriate solvent, such as a halogenated hydrocarbon, e.g. methylene chloride or 1,2,-dichloroethane, and optionally a carbonic acid, e.g. acetic acid, at preferred temperatures between -10 °C and 50 °C, e.g. from 0 °C to room temperature; if required, the subsequent removal of protecting groups takes place e.g. as described above under (A).

The condensation of an acid of the formula II, or a reactive derivative thereof, under (C) preferably takes place under customary condensation conditions, where among the possible reactive derivatives of an acid of the formula II reactive esters (such as the hydroxybenzotriazole (HOBT), pentafluorophenyl, 4-nitrophenyl or N-hydroxysuccinimide ester), acid halogenides (such as the acid chloride or bromide) or reactive anhydrides (such

as mixed anhydrides with lower alkanoic acids or symmetric anhydrides) are preferred. Reactive carbonic acid derivatives can also and preferably be formed in situ. The reaction is carried out by dissolving the compounds of formulae II and VI in a suitable solvent, for example a halogenated hydrocarbon, such as methylene chloride, *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-methyl-2-pyrrolidone, methylene chloride, or a mixture of two or more such solvents, and by the addition of a suitable base, for example triethylamine, diisopropylethylamine (DIEA) or *N*-methylmorpholine and, if the reactive derivative of the acid of the formula II is formed *in situ*, a suitable coupling agent that forms a preferred reactive derivative of the carbonic acid of formula III *in situ*, for example dicyclohexylcarbodiimide/1-hydroxybenzotriazole (DCC/ HOBT); bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl); *O*-(1,2-dihydro-2-oxo-1-pyridyl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TPTU); O-benzotriazol-1-yl)-N,N,N', N'-tetramethyluronium tetrafluoroborate (TBTU); (benzotriazol-1-yloxy)-tripyrrolidinophosphonium-hexafluorophosphate (PyBOP), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride/hydroxybenzotriazole or/1-hydroxy-7-azabenzotriazole (EDC/HOBT or EDC/HOAt) or HOAt alone, or with (1-chloro-2-methyl-propenyl)-dimethylamine. For review of some other possible coupling agents, see e.g. Klauser; Bodansky, *Synthesis* **1972**, 453-463. The reaction mixture is preferably stirred at a temperature of between approximately -20 and 50 °C, especially between 0 °C and 30 °C, e.g. at room temperature. The reaction may preferably carried out under an inert gas, e.g. nitrogen or argon. If required, the subsequent removal of protecting groups takes place e.g. as described above under (A).

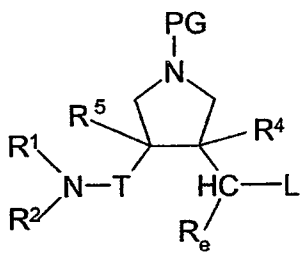
The esterification under (D) can be carried out under comparable reaction conditions as described for the condensation under (C) described in the preceding paragraph, and also the reactive derivatives of the acid of the formula II may be as described there, if in the compound of the formula VII X is hydroxy. Where X is a leaving group, especially halogen, the reaction takes place in the presence of a base. If required, the subsequent removal of protecting groups takes place e.g. as described above under (A).

The condensation under reaction (E) (i) preferably takes place under conditions as mentioned above for reaction (C), the esterification under reaction (E) (ii) with compounds of the formula VII wherein X is OH preferably takes place under conditions mentioned above for reaction (D), the reaction (e) (ii) with compounds of the formula VII wherein X is a leaving group, preferably halogen, can take place in the presence of a base.

Optional Reactions and Conversions

Compounds of the formula I, or protected forms thereof directly obtained according to any one of the preceding procedures (meaning that, if conversion is desired, a removal of protecting groups is not required under (A), (B), (C), (D) or (E) or after introducing protecting groups anew, which are included subsequently as starting materials for conversions as well even if not mentioned specifically, can be converted into different compounds of the formula I according to known procedures, where required after removal of protecting groups.

For example, a compound of the formula I wherein R_1, R_2, R_4, R_5 and T are as defined for compounds of the formula I above or below and wherein R^3 is a group of the formula (a) mentioned above wherein R_e is as defined for a compound of the formula I and R_a is hydrogen (which compound may be used in free or preferably in protected form, e.g. a compound of the formula III given above) may be converted into the corresponding compound of the formula VIII,



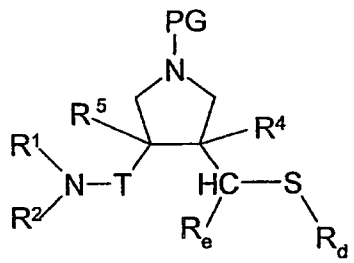
(VIII)

wherein R_e, R_1, R_2, R_4, R_5 and T are as just defined, PG is a protecting group and L is a leaving group, especially a C_1-C_7-alkanesulfonyloxy, such as methanesulfonyloxy, or arylsulfonyloxy, such as toluenesulfonyloxy, preferably by reaction with the corresponding alkane- or arylsulfonylhalogenide, e.g. –chloride, under customary conditions, e.g. in the absence or presence of an appropriate solvent, such as an ether or a halogenated hydrocarbon, in the presence of a tertiary nitrogen base, such as triethylamine, at temperatures e.g. from –20 °C to the reflux temperature of the reaction mixture, giving a corresponding compound of the formula VIII; the latter can then be deprotected to give the corresponding compound of the formula I, or reacted with a mercapto compound of the formula X,

$$R_d\text{-SH} \qquad (X)$$

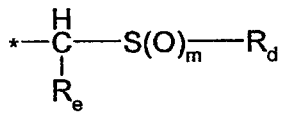
wherein R_d is a moiety as defined as for a compound of the formula I other than of the formula $-N(R_a)(R_b)$, to give a corresponding compound of the formula XI,

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(XI)

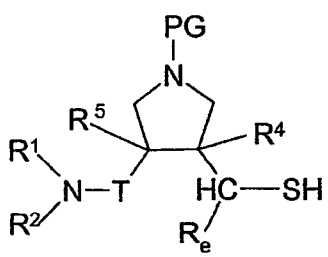
wherein R_1, R_2, R_4, R_5 and T are as just defined and PG is a protecting group, which may then be deprotected to give a compound of the formula I wherein R^3 is a moiety of the formula (c)



(c)

wherein R_e is as defined for a compound of the formula I, m is 0 (zero) and R_d is as defined for a compound of the formula X; or converted by oxidation, e.g. with an organic peroxide, such as m-chloro-perbenzoic acid, in an appropriate solvent, e.g. dimethylformamide, tetrahydrofurane or methylene chloride, to the corresponding compound wherein m is 2 which after deprotection gives the corresponding compound of the formula I.

Alternatively, a compound of the formula I wherein R_1, R_2, R_4, R_5 and T are as defined for compounds of the formula I above or below and wherein R^3 is a group of the formula (a) mentioned above wherein R_e is as defined for a compound of the formula I and R_a is hydrogen (which compound may be used in free or preferably in protected form, e.g. a compound of the formula III given above) may be converted into a compound of the formula VIII as described above which is then reacted with a C_1-C_7-alkanoyl-thiolate, e.g. an alkalimetal (such as sodium) thiolate, to the corresponding compound of the formula XI given above wherein R_d is C_1-C_7-alkanoyl, such as acetyl, which is then hydrolyzed, e.g. with lithium hydroxide, under customary conditions to the corresponding free mercapto compound of the formula XIA,



(XIA)

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which is then either

(i) reacted with a compound of the formula XA,

R_d-Hal (XA)

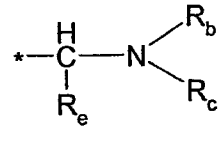
wherein Hal is halo and R_d has a meaning as defined herein other than -N($R_b$$R_c$), to a corresponding protected version of a compound of the formula I which can then be deprotected to give the corresponding compound of the formula I wherein R_d is as defined for a compound of the formula XA, or which can first be oxidised to a protected version of a compound of the formula I wherein m is 1 or preferably 2, for example with a peroxide, such as m-chloro-perbenzoic acid, and then deprotected to give the corresponding compound of the formula I; or

(ii) oxidized with a peroxide, such as hydrogen peroxide, and subsequently reacted with a halogenating agent, such as phosphorous oxychloride or oxalyl chloride, to the corresponding compound wherein instead of the SH group an $S(O)_2$-Hal group, e.g. wherein Hal is halo, especially chloro, is present, which can then be reacted with a compound of the formula VI

R_b-NH-R_c (VI)

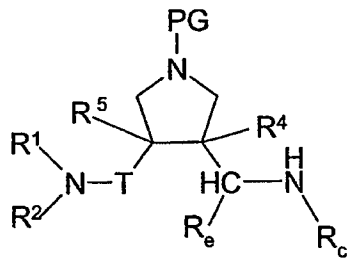
as defined above to give, after deprotection, a corresponding compound of the formula I wherein R_d is a group of the formula –N(R_b)(R_c).

In a compound of the formula I wherein R^3 is a moiety of the formula (b)



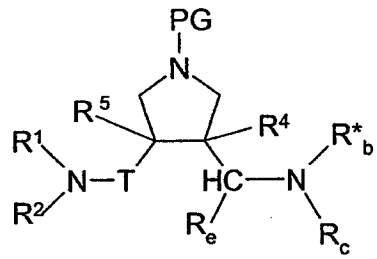
(b)

wherein R_e is as defined for a compound of the formula I, R_c is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl and R_b is hydrogen, or preferably a protected derivative thereof, e.g. of the formula XII,



(XII)

wherein PG is a protecting group and the other moieties are as defined for a compound of the formula I, can be converted into the acylated compound of the formula XIII,



(XIII)

wherein R^*_b is acyl and the other moieties are as defined for a compound of the formula XII, by reaction with a corresponding acid of the formula XIV,

$$R^*_b\text{-OH} \qquad \text{(XIV)}$$

wherein R^*_b is acyl, or a reactive derivative thereof. Removal of the protecting group(s) then leads to the corresponding compound of the formula I wherein R^3 is a moiety of the formula (b) as just given wherein R_e and R_c are as defined for a compound of the formula XII and R_b is acyl.

An oxo group in a compound of the formula I, e.g. carbonyl as T, may be converted to the corresponding thioxo, e.g. thiocarbonyl, group by reaction with Lawesson`s reagent under customary reaction conditions.

Salts of compounds of formula I having at least one salt-forming group may be prepared in a manner known *per se*. For example, salts of compounds of formula I having acid groups may be formed, for example, by treating the compounds with metal compounds, such as alkali metal salts of suitable organic carboxylic acids, e.g. the sodium salt of 2-ethylhexanoic acid, with organic alkali metal or alkaline earth metal compounds, such as the corresponding hydroxides, carbonates or hydrogen carbonates, such as sodium or potassium hydroxide, carbonate or hydrogen carbonate, with corresponding calcium compounds or with ammonia or a suitable organic amine, stoichiometric amounts or only a small excess of the salt-forming

agent preferably being used. Acid addition salts of compounds of formula I are obtained in customary manner, e.g. by treating the compounds with an acid or a suitable anion exchange reagent. Internal salts of compounds of formula I containing acid and basic salt-forming groups, e.g. a free carboxy group and a free amino group, may be formed, e.g. by the neutralisation of salts, such as acid addition salts, to the isoelectric point, e.g. with weak bases, or by treatment with ion exchangers.

A salt of a compound of the formula I can be converted in customary manner into the free compound; metal and ammonium salts can be converted, for example, by treatment with suitable acids, and acid addition salts, for example, by treatment with a suitable basic agent. In both cases, suitable ion exchangers may be used.

Stereoisomeric mixtures, e.g. mixtures of diastereomers, can be separated into their corresponding isomers in a manner known per se by means of appropriate separation methods. Diastereomeric mixtures for example may be separated into their individual diastereomers by means of fractionated crystallization, chromatography, solvent distribution, and similar procedures. This separation may take place either at the level of one of the starting compounds or in a compound of formula I itself. Enantiomers may be separated through the formation of diastereomeric salts, for example by salt formation with an enantiomer-pure chiral acid, or by means of chromatography, for example by HPLC, using chromatographic substrates with chiral ligands.

Intermediates and final products can be worked up and/or purified according to standard methods, e.g. using chromatographic methods, distribution methods, (re-) crystallization, and the like. Some possible methods that can also be used with other compounds analogously can be found in the Examples.

Starting Materials

In the subsequent description of starting materials (which term also includes intermediates) and their synthesis, R^1, R^2, R^3, R^4, R^5, T, m, R_a, R_b, R_c, R_d, R_e, R_f and PG have the meanings given above or in the Examples for the respective starting materials or intermediates, if not indicated otherwise directly or by the context. Protecting groups, if not specifically mentioned, can be introduced and removed at appropriate steps in order to prevent functional groups, the reaction of which is not desired in the corresponding reaction step or steps, from participating in a reaction, employing protecting groups, methods for their

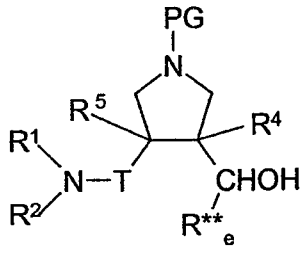
introduction and their removal are as described above or below, e.g. in the references mentioned under "General Process Conditions". The person skilled in the art will readily be able to decide whether and which protecting groups are useful or required and at which stage it is appropriate to introduce , exchange and/or remove protecting groups.

A compound of the formula II wherein R^*_e is hydrogen (which is a compound of the formula V wherein R^*_e is hydrogen) can be obtained from a compound of the formula IIB or of the formula XV given below by reduction of the (in the case of formula XV esterified, e.g. by C_1-C_7-alkyloxy) carboxy function, e.g. with an appropriate complex hydride, such as borane-dimethylsulfide complex, in an appropriate solvent, such as an ether, e.g. tetrahydrofurane, at preferred temperatures between –50 °C and the reflux temperature of the reaction mixture, e.g. at –30 to 60 °C.

A compound of the formula II wherein R^*_e is unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or (especially) substituted or preferably unsubstituted C_1-C_7-alkyl (which is a compound of the formula V wherein R_e is unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or (especially) substituted or preferably unsubstituted C_1-C_7-alkyl) can, for example, be obtained from a compound of the formula V wherein R^*_e is hydrogen by reaction with a grignard reagent of the formula XXII,

$$R^{**}_e\text{-Mg-Hal} \qquad \text{(XXII)}$$

wherein R^{**}_e is unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or (especially) substituted or preferably unsubstituted C_1-C_7-alkyl and Hal is halo, especially chloro or bromo, under customary reaction conditions, e.g. in an ether, such as diethylether, at preferred temperatures from 0 °C to the reflux temperature of the reaction mixture, to give a compound of the formula IIIA,

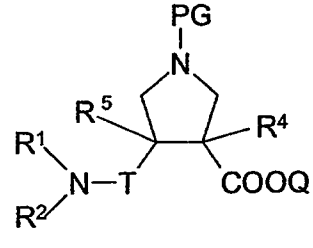


(IIIA)

wherein R^{**}_e is as just described (which is a compound of the formula III wherein R^*_e is as just defined for R^{**}_e); which is then oxidized, e.g. in the presence of an appropriate oxidant, such as Dess-Martin-periodinane, in an appropriate solvent, e.g. a halogenated hydrocarbon, e.g. methylene chloride, at preferred temperatures from 0 °C to 50 °C, e.g. at room temperature, to give the corresponding compound of the formula II or V.

Alternatively, a compound of the formula II wherein R^*_e is unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or (especially) substituted or preferably unsubstituted C_1-C_7-alkyl can be reacted in the presence of a condensation agent, e.g. under reaction conditions and with reagents as described under process variants (C) and (D) above, with N,O-dimethyl hydroxylamine to form the corresponding Weinreb amide which can then directly be reacted with a Grignard reagent of the formula XXII as described above to a corresponding compound of the formula II or V.

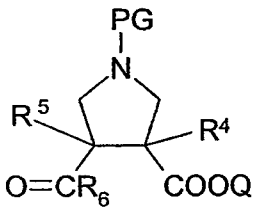
A compound of the formula IIB (which is a compound of the formula II wherein R^*_e is hydroxy) can be prepared from a corresponding ester of the formula XV,



(XV)

wherein Q is an organic moiety, preferably substituted or especially unsubstituted C_1-C_7-alkyl, by hydrolysis in the presence of a base, e.g. an alkaline metal hydroxide, such as lithium hydroxide, in an appropriate solvent, e.g. a hydroxy lower alkane, such as methanol, in the presence of water and preferably at temperatures e.g. from 0 to 50 °C.

A compound of the formula XV wherein T is methylene or methylene mono-substituted by alkyl (-[C(H)(alkyl)]-) can, for example, be obtained by reacting an aldehyde or keto compound of the formula XVI,



(XVI)

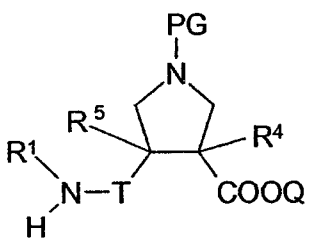
wherein Q is as described for a compound of the formula XV and R_6 is alkyl or preferably hydrogen with an amine of the formula XVII,

$$R^1\text{-}NH\text{-}R^2 \qquad \text{(XVII)}$$

under conditions of reductive amination, e.g. under the reaction conditions described for reaction (B) above. If instead of a compound of the formula XVII a compound of the formula XVII*,

$$H_2\text{-}N\text{-}R_1 \qquad \text{(XVII*)}$$

is used, a compound of the formula XV* results,



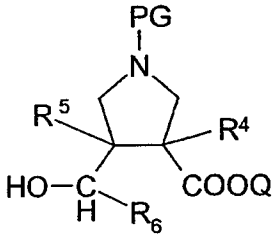
(XV*)

wherein Q is as defined for a compound of the formula XV, which can then be converted into a compound of the formula XV by reaction with a compound of the formula XVIII,

$$R_2\text{-}Y \qquad \text{(XVIII)}$$

wherein Y, if R_2 is acyl, is either hydroxy or the compound is a reactive derivative, e.g. wherein Y is halo or an activating group formed in situ, preferably under conditions analogous to those in reaction (C) above; or Y, if R_2 is one of the moieties defined for R_2 in compounds of the formula I other than acyl, is a leaving group, e.g. as defined for X in a compound of the formula IV above and under reaction conditions analogous to those described above for the reaction under (A) (i).

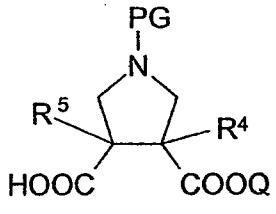
A compound of the formula XVI wherein R_6 is alkyl or preferably hydrogen can, for example, be obtained from a hydroxy compound of the formula XIX,



(XIX)

wherein R_6 is alkyl or preferably hydrogen and Q is as defined for a compound of the formula XV by oxidation to the corresponding oxo compound of the formula XVI which preferably takes place in the presence of an appropriate oxidant, such as Dess-Martin-periodinane, in an appropriate solvent, e.g. a halogenated hydrocarbon, e.g. methylene chloride, at preferred temperatures from 0 °C to 50 °C, e.g. at room temperature.

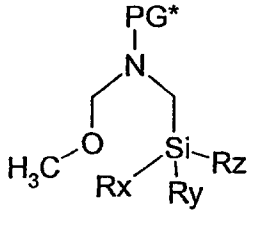
A hydroxy compound of the formula XIX wherein R_6 is hydrogen can, for example, be obtained from a compound of the formula XX,



(XX)

wherein Q is as defined for a compound of the formula XV by reduction in the presence of an appropriate complex hydride, e.g. borane dimethylsulfide complex, in an appropriate solvent, such as an ether, e.g. tetrahydrofurane, at preferred temperatures between –50 ° and the reflux temperature of the reaction mixture, e.g. at –30 to 60 °C.

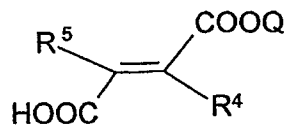
A compound of the formula XX may, inter alia, be obtained by reacting a compound of the formula XXI,



(XXI)

wherein PG* is a protecting group that withstands the reaction, e.g. benzyl, and each of Rx, Ry and Rz are alkyl, preferably C1-C7-alkyl, especially methyl, with a fumaric acid derivative of the formula XXII,

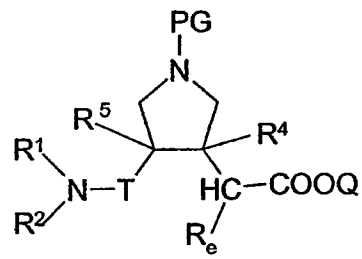
120



(XXI)

wherein each of R^4 and R^5 preferably has one of the meanings given for R^4 and R^5 other than hydroxy, more preferably is C_1-C_7-alkyl, e.g. methyl or ethyl, or is hydrogen, in the presence of an acid, e.g. trifluoroacetic acid, in an appropriate solvent, such as y halogenated hydrocarbon, e.g. methylene chloride, at preferred temperatures e.g. in the range from –30 to 50 °C, yielding the corresponding compound of the formula XX wherein preferably the protecting group PG* can be replaced with a different protecting group PG useful for subsequent reactions, such as tert-butoxycarbonyl, for example benzyl PG* can be removed with hydrogen in the presence of a hydrogenation catalyst, especially a noble metal catalyst, preferably on a carrier material, such as charcoal, e.g. Pd/C, in an appropriate solvent, such as an alcohol, e.g. ethanol, at temperatures e.g. from –10 to 60 °C, and tert-butoxycarbonyl may be introduced in the same step or subsequently by reaction with tert-butoxycarbonic anhydride.

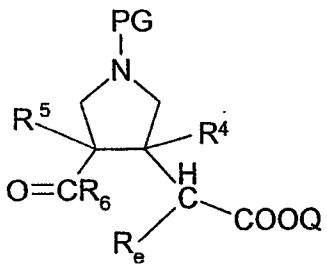
A compound of the formula IIA can, for example, be prepared from a corresponding ester of the formula XVA,



(XVA)

wherein Q is an organic moiety, preferably substituted or especially unsubstituted C_1-C_7-alkyl, by hydrolysis in the presence of a base, e.g. an alkaline metal hydroxide, such as lithium hydroxide, in an appropriate solvent, e.g. a hydroxy lower alkane, such as methanol, in the presence of water and preferably at temperatures e.g. from 0 to 50 °C.

A compound of the formula XVA wherein T is methylene or methylene mono-substituted by alkyl (-[C(H)(alkyl)]-) can, for example, be obtained by reacting an aldehyde or keto compound of the formula XVIA,



(XVIA)

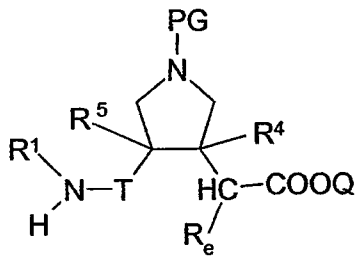
wherein Q is as described for a compound of the formula XVA and R_6 is alkyl or preferably hydrogen with an amine of the formula XVII,

$$R^1\text{-NH-}R^2 \qquad \text{(XVII)}$$

under conditions of reductive amination, e.g. under the reaction conditions described for reaction (B) above. If instead of a compound of the formula XVII a compound of the formula XVII*,

$$H_2\text{-N-}R_1 \qquad \text{(XVII*)}$$

is used, a compound of the formula XVA* results,



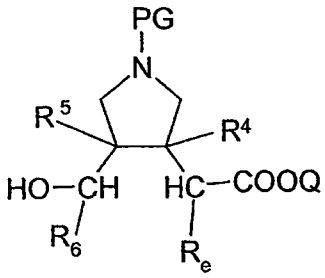
(XVA*)

wherein Q is as defined for a compound of the formula XVA, which can then be converted into a compound of the formula XVA by reaction with a compound of the formula XVIII,

$$R_2\text{-Y} \qquad \text{(XVIII)}$$

wherein Y, if R_2 is acyl, is either hydroxy or the compound is a reactive derivative, e.g. wherein Y is halo or an activating group formed in situ, preferably under conditions analogous to those in reaction (C) above; or Y, if R_2 is one of the moieties defined for R_2 in compounds of the formula I other than acyl, is a leaving group, e.g. as defined for X in a compound of the formula IV above and under reaction conditions analogous to those described above for the reaction under (A) (i).

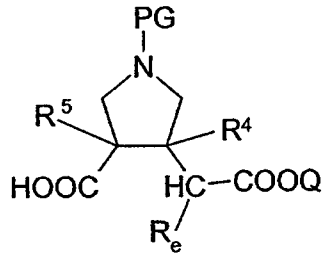
A compound of the formula XVIA wherein R_6 is alkyl or preferably hydrogen can, for example, be obtained from a hydroxy compound of the formula XIXA,



(XIXA)

wherein R_6 is alkyl or preferably hydrogen and Q is as defined for a compound of the formula XVA by oxidation to the corresponding oxo compound of the formula XVIA which preferably takes place in the presence of an appropriate oxidant, such as Dess-Martin-periodinane, in an appropriate solvent, e.g. a halogenated hydrocarbon, e.g. methylene chloride, at preferred temperatures from 0 °C to 50 °C, e.g. at room temperature.

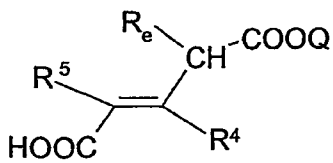
A hydroxy compound of the formula XIXA wherein R_6 is hydrogen can, for example, be obtained from a compound of the formula XXA,



(XXA)

wherein Q is as defined for a compound of the formula XV by reduction in the presence of an appropriate complex hydride, e.g. borane dimethylsulfide complex, in an appropriate solvent, such as an ether, e.g. tetrahydrofurane, at preferred temperatures between –50 ° and the reflux temperature of the reaction mixture, e.g. at –30 to 60 °C.

A compound of the formula XXA may, inter alia, be obtained by reacting a compound of the formula XXI, as described above, with a fumaric acid derivative of the formula XXIA,



(XXIA)wherein each of R^4 and R^5 preferably has one of the meanings given for R^4 and R^5 other than hydroxy, more preferably is C_1-C_7-alkyl, e.g. methyl or ethyl, or is hydrogen, in the presence of an acid, e.g. trifluoroacetic acid, in an appropriate solvent,

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such as y halogenated hydrocarbon, e.g. methylene chloride, at preferred temperatures e.g. in the range from –30 to 50 °C, yielding the corresponding compound of the formula XXA wherein preferably the protecting group PG* can be replaced with a different protecting group PG useful for subsequent reactions, such as tert-butoxycarbonyl, for example benzyl PG* can be removed with hydrogen in the presence of a hydrogenation catalyst, especially a noble metal catalyst, preferably on a carrier material, such as charcoal, e.g. Pd/C, in an appropriate solvent, such as an alcohol, e.g. ethanol, at temperatures e.g. from –10 to 60 °C, and tert-butoxycarbonyl may be introduced in the same step or subsequently by reaction with tert-butoxycarbonic anhydride.

A compound of the formula IIA may also be obtained by reacting a compound of the formula VIII as described above with a cyanide salt, e.g. an alkali metal cyanide, such as sodium or potassium cyanide, to the corresponding compound wherein instead of the –C(H)(R_e)-L group a –C(H)(R_e)-CN group is present, followed by hydrolysis with a base, such as sodium hydroxide, or under mild conditions by reaction first with H_2S resulting in a corresponding thioamide which can then be hydrolysed under mild conditions to give a corresponding compound of the formula IIA.

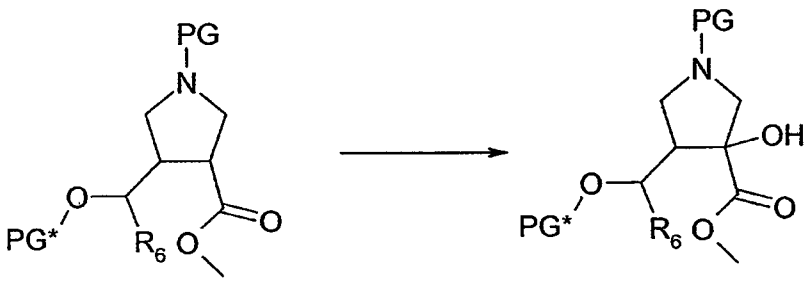
A compound of the formula XV or XVA wherein T is carbonyl (and Q is as defined for compounds of the formula XV above) can, for example, be obtained by reacting a compound of the formula XX or XXA, respectively, as defined above, or a reactive derivative thereof, under conditions analogous to those described above for the condensation reaction under process variant (C) with a compound of the formula XVII as defined above.

In the preceding starting materials (and final products), R^4 and R^5 are preferably hydrogen, with less preference unsubstituted or substituted alkyl, esterified or etherified hydroxy, with still less preference (in the intermediates preferably protected) hydroxy.

Hydroxy R^4 and/or R^5 can be introduced into starting materials at various stages, e.g. in (preferably appropriately protected) compounds of the formula XV,
for example by treatment with a strong base to remove the hydrogen to be substituted by R^4 or R^5, such as lithium hexamethyldisialazide (LHMDS) or preferably lithium diisopropylamide in tetrahydrofuran at low temperatures, e.g. from –100 to –50 °C, such as at –78 °C,

followed by oxidation e.g. by addition of an oxaziridine derivative according to Davis (e.g. 2-tert-butoxycarbonyl-3-trichloromethyl-oxaziridine or 2-(phenylsulfonyl or tolylsulfonyl)-3-phenyl-oxaziridine or (e.g. for stereoselective synthesis) (+)- or (-)-(camphorsulfonyl)oxaziridine) to give the corresponding hydroxy compound.

An alternative is the transformation on the following O-protected alcohol shown on the left (a compound of the formula XIX) to give an intermediate (shown on the right, also a compound of the formula XIX) that can be used either to build a final pyrrolidine where R^5 or R^4 are OH or etherified or esterified hydroxy depending on the sequence of reactions used:



wherein in both formulae PG* is a hydroxy protecting group, under comparable reacrtion conditions as just mentioned or other customary conditions.

Hydroxy R^4 and/or R^5 may then further be esterified or etherified according to standard procedures to give the corresponding compounds wherein $R^4$and/or R^5 is esterified or etherified hydroxy.

Other starting materials, such as also the starting materials of the formula IV, IV*, VI, VII, X and XIV are known in the art, can be prepared according to methods that are known in the art and/or are commercially available.

General Process Conditions

The following applies in general to all processes mentioned hereinbefore and hereinafter, while reaction conditions specifically mentioned above or below are preferred:

In any of the reactions mentioned hereinbefore and hereinafter, protecting groups may be used where appropriate or desired, even if this is not mentioned specifically, to protect functional groups that are not intended to take part in a given reaction, and they can be introduced and/or removed at appropriate or desired stages. Reactions comprising the use

of protecting groups are therefore included as possible wherever reactions without specific mentioning of protection and/or deprotection are described in this specification.

Within the scope of this disclosure only a readily removable group that is not a constituent of the particular desired end product of formula I is designated a "protecting group", unless the context indicates otherwise. The protection of functional groups by such protecting groups, the protecting groups themselves, and the reactions appropriate for their introduction and removal are described for example in standard reference works, such as J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999, in "The Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and New York 1981, in "Methoden der organischen Chemie" (*Methods of Organic Chemistry*), Houben Weyl, 4th edition, Volume 15/I, Georg Thieme Verlag, Stuttgart 1974, in H.-D. Jakubke and H. Jeschkeit, "Aminosäuren, Peptide, Proteine" (*Amino acids, Peptides, Proteins*), Verlag Chemie, Weinheim, Deerfield Beach, and Basel 1982, and in Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate" (*Chemistry of Carbohydrates: Monosaccharides and Derivatives*), Georg Thieme Verlag, Stuttgart 1974. A characteristic of protecting groups is that they can be removed readily (i.e. without the occurrence of undesired secondary reactions) for example by solvolysis, reduction, photolysis or alternatively under physiological conditions (e.g. by enzymatic cleavage).

All the above-mentioned process steps can be carried out under reaction conditions that are known per se, preferably those mentioned specifically, in the absence or, customarily, in the presence of solvents or diluents, preferably solvents or diluents that are inert towards the reagents used and dissolve them, in the absence or presence of catalysts, condensation or neutralizing agents, for example ion exchangers, such as cation exchangers, e.g. in the H^+ form, depending on the nature of the reaction and/or of the reactants at reduced, normal or elevated temperature, for example in a temperature range of from about -100 °C to about 190°C, preferably from approximately -80°C to approximately 150°C, for example at from -80 to -60°C, at room temperature, at from -20 to 40 °C or at reflux temperature, under atmospheric pressure or in a closed vessel, where appropriate under pressure, and/or in an inert atmosphere, for example under an argon or nitrogen atmosphere.

The solvents from which those solvents that are suitable for any particular reaction may be selected include those mentioned specifically or, for example, water, esters, such as lower

alkyl-lower alkanoates, for example ethyl acetate, ethers, such as aliphatic ethers, for example diethyl ether, or cyclic ethers, for example tetrahydrofurane or dioxane, liquid aromatic hydrocarbons, such as benzene or toluene, alcohols, such as methanol, ethanol or 1- or 2-propanol, nitriles, such as acetonitrile, halogenated hydrocarbons, e.g. as methylene chloride or chloroform, acid amides, such as dimethylformamide or dimethyl acetamide, bases, such as heterocyclic nitrogen bases, for example pyridine or N-methylpyrrolidin-2-one, carboxylic acid anhydrides, such as lower alkanoic acid anhydrides, for example acetic anhydride, cyclic, linear or branched hydrocarbons, such as cyclohexane, hexane or isopentane, or mixtures of these, for example aqueous solutions, unless otherwise indicated in the description of the processes. Such solvent mixtures may also be used in working up, for example by chromatography or partitioning.

The invention relates also to those forms of the processes in which a compound obtainable as intermediate at any stage of the process is used as starting material and the remaining process steps are carried out, or in which a starting material is formed under the reaction conditions or is used in the form of a derivative, for example in protected form or in the form of a salt, or a compound obtainable by the process according to the invention is produced under the process conditions and processed further in situ. In the processes of the present invention those starting materials are preferably used which result in compounds of formula I described as being preferred. Special preference is given to reaction conditions that are identical or analogous to those mentioned in the Examples. The invention relates also to novel starting compounds and intermediates described herein, especially those leading to novel compounds of the formula I or compounds of the formula I mentioned as preferred herein.

Pharmaceutical use, pharmaceutical preparations and methods

As described above, the compounds of the present invention are inhibitors of renin activity and, thus, may be of use for the treatment of hypertension, atherosclerosis, unstable coronary syndrome, congestive heart failure, cardiac hypertrophy, cardiac fibrosis, cardiomyopathy postinfarction, unstable coronary syndrome, diastolic dysfunction, chronic kidney disease, hepatic fibrosis, complications resulting from diabetes, such as nephropathy, vasculopathy and neuropathy, diseases of the coronary vessels, restenosis following angioplasty, raised intra-ocular pressure, glaucoma, abnormal vascular growth and/or hyperaldosteronism, and/or further cognitive impairment, alzheimers, dementia, anxiety states and cognitive

disorders, and the like. Hypertension, at least as one component of the disease to be treated, is especially preferred, meaning that hypertension alone or in combination with one or more (especially of the mentioned) other diseases may be treated (prophylactically and/or therapeutically).

The present invention further provides pharmaceutical compositions comprising a therapeutically effective amount of a pharmacologically active compound of the instant invention, alone or in combination with one or more pharmaceutically acceptable carriers.

The pharmaceutical compositions according to the present invention are those suitable for enteral, such as oral or rectal, transdermal and parenteral administration to mammals, including man, to inhibit renin activity, and for the treatment of conditions associated with (especially inappropriate) renin activity. Such conditions include hypertension, atherosclerosis, unstable coronary syndrome, congestive heart failure, cardiac hypertrophy, cardiac fibrosis, cardiomyopathy postinfarction, unstable coronary syndrome, diastolic dysfunction, chronic kidney disease, hepatic fibrosis, complications resulting from diabetes, such as nephropathy, vasculopathy and neuropathy, diseases of the coronary vessels, restenosis following angioplasty, raised intra-ocular pressure, glaucoma, abnormal vascular growth and/or hyperaldosteronism, and/or further cognitive impairment, alzheimers, dementia, anxiety states and cognitive disorders and the like. Especially preferred is a disease which comprises hypertension, more especially hypertension itself, where treatment with a pharmaceutical composition or the use of a compound of the formula I for its synthesis is useful prophylactically and/or (preferably) therapeutically.

Thus, the pharmacologically active compounds of the invention may be employed in the manufacture of pharmaceutical compositions comprising an effective amount thereof in conjunction or admixture with excipients or carriers suitable for either enteral or parenteral application. Preferred are tablets and gelatin capsules comprising the active ingredient together with:

a) diluents, e.g., lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine;

b) lubricants, e.g., silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also

c) binders, e.g., magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and or polyvinylpyrrolidone; if desired

d) disintegrants, e.g., starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or
e) absorbants, colorants, flavors and sweeteners.

Injectable compositions are preferably aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions.

Said compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. Said compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1-75%, preferably about 1-50%, of the active ingredient.

Suitable formulations for transdermal application include a therapeutically effective amount of a compound of the invention with carrier. Advantageous carriers include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. Characteristically, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound of the skin of the host at a controlled and pre-determined rate over a prolonged period of time, and means to secure the device to the skin.

Accordingly, the present invention provides pharmaceutical compositions as described above for the treatment of conditions mediated by renin activity, preferably, hypertension, atherosclerosis, unstable coronary syndrome, congestive heart failure, cardiac hypertrophy, cardiac fibrosis, cardiomyopathy postinfarction, unstable coronary syndrome, diastolic dysfunction, chronic kidney disease, hepatic fibrosis, complications resulting from diabetes, such as nephropathy, vasculopathy and neuropathy, diseases of the coronary vessels, restenosis following angioplasty, raised intra-ocular pressure, glaucoma, abnormal vascular growth and/or hyperaldosteronism, and/or further cognitive impairment, alzheimers, dementia, anxiety states and cognitive disorders, as well as methods of their use.

The pharmaceutical compositions may contain a therapeutically effective amount of a compound of the formula I as defined herein, either alone or in a combination with another therapeutic agent, e.g., each at an effective therapeutic dose as reported in the art. Such therapeutic agents include:

a) antidiabetic agents such as insulin, insulin derivatives and mimetics; insulin secretagogues such as the sulfonylureas, e.g., Glipizide, glyburide and Amaryl; insulinotropic sulfonylurea receptor ligands such as meglitinides, e.g., nateglinide and repaglinide; peroxisome proliferator-activated receptor (PPAR) ligands; protein tyrosine phosphatase-1B (PTP-1B) inhibitors such as PTP-112; GSK3 (glycogen synthase kinase-3) inhibitors such as SB-517955, SB-4195052, SB-216763, NN-57-05441 and NN-57-05445; RXR ligands such as GW-0791 and AGN-194204; sodium-dependent glucose cotransporter inhibitors such as T-1095; glycogen phosphorylase A inhibitors such as BAY R3401; biguanides such as metformin; alpha-glucosidase inhibitors such as acarbose; GLP-1 (glucagon like peptide-1), GLP-1 analogs such as Exendin-4 and GLP-1 mimetics; and DPPIV (dipeptidyl peptidase IV) inhibitors such as LAF237;

b) hypolipidemic agents such as 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, e.g., lovastatin, pitavastatin, simvastatin, pravastatin, cerivastatin, mevastatin, velostatin, fluvastatin, dalvastatin, atorvastatin, rosuvastatin and rivastatin; squalene synthase inhibitors; FXR (farnesoid X receptor) and LXR (liver X receptor) ligands; cholestyramine; fibrates; nicotinic acid and aspirin;

c) anti-obesity agents such as orlistat; and

d) anti-hypertensive agents, e.g., loop diuretics such as ethacrynic acid, furosemide and torsemide; angiotensin converting enzyme (ACE) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perinodopril, quinapril, ramipril and trandolapril; inhibitors of the Na-K-ATPase membrane pump such as digoxin; neutralendopeptidase (NEP) inhibitors; ACE/NEP inhibitors such as omapatrilat, sampatrilat and fasidotril; angiotensin II antagonists such as candesartan, eprosartan, irbesartan, losartan, telmisartan and valsartan, in particular valsartan; β-adrenergic receptor blockers such as acebutolol, atenolol, betaxolol, bisoprolol, metoprolol, nadolol, propranolol, sotalol and timolol; inotropic agents such as digoxin, dobutamine and milrinone; calcium channel blockers such as amlodipine, bepridil, diltiazem, felodipine, nicardipine, nimodipine, nifedipine, nisoldipine and verapamil; aldosterone receptor antagonists; and aldosterone synthase inhibitors.

Other specific anti-diabetic compounds are described by Patel Mona in *Expert Opin Investig Drugs*, 2003, 12(4), 623-633, in the figures 1 to 7, which are herein incorporated by reference. A compound of the present invention may be administered either simultaneously, before or after the other active ingredient, either separately by the same or different route of administration or together in the same pharmaceutical formulation.

The structure of the therapeutic agents identified by code numbers, generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g., Patents International (e.g. IMS World Publications). The corresponding content thereof is hereby incorporated by reference.

Accordingly, the present invention provides pharmaceutical products or compositions comprising a therapeutically effective amount of a compound of the invention alone or in combination with a therapeutically effective amount of another therapeutic agent, preferably selected from anti-diabetics, hypolipidemic agents, anti-obesity agents or anti-hypertensive agents, most preferably from antidiabetics, anti-hypertensive agents or hypolipidemic agents as described above.

The present invention further relates to pharmaceutical compositions as described above for use as a medicament.

The present invention further relates to use of pharmaceutical compositions or combinations as described above for the preparation of a medicament for the treatment of conditions mediated by (especially inappropriate) renin activity, preferably, hypertension, atherosclerosis, unstable coronary syndrome, congestive heart failure, cardiac hypertrophy, cardiac fibrosis, cardiomyopathy postinfarction, unstable coronary syndrome, diastolic dysfunction, chronic kidney disease, hepatic fibrosis, complications resulting from diabetes, such as nephropathy, vasculopathy and neuropathy, diseases of the coronary vessels, restenosis following angioplasty, raised intra-ocular pressure, glaucoma, abnormal vascular growth and/or hyperaldosteronism, and/or further cognitive impairment, alzheimers, dementia, anxiety states and cognitive disorders, and the like.

Thus, the present invention also relates to a compound of formula I for use as a medicament, to the use of a compound of formula I for the preparation of a pharmaceutical composition for the prevention and/or treatment of conditions mediated by (especially inappropriate) renin activity, and to a pharmaceutical composition for use in conditions mediated by (especially inappropriate) renin activity comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier material therefore.

The present invention further provides a method for the prevention and/or treatment of conditions mediated by (especially inappropriate) renin activity, which comprises administering

a therapeutically effective amount of a compound of the present invention to a warm-blooded animal, especially a human, in need of such treatment.

A unit dosage for a mammal of about 50-70 kg may contain between about 1 mg and 1000 mg, advantageously between about 5-600 mg of the active ingredient. The therapeutically effective dosage of active compound is dependent on the species of warm-blooded animal (especially mammal, more especially human), the body weight, age and individual condition, on the form of administration, and on the compound involved.

In accordance with the foregoing the present invention also provides a pharmaceutical product comprising a therapeutic combination, e.g., a kit, kit of parts, e.g., for use in any method as defined herein, comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, to be used concomitantly or in sequence with at least one pharmaceutical composition comprising at least another therapeutic agent, preferably selected from anti-diabetic agents, hypolipidemic agents, anti-obesity agents or anti-hypertensive agents. The kit may comprise instructions for its administration.

Similarly, the present invention provides a kit of parts comprising: (i) a pharmaceutical composition comprising a compound of the formula I according to the invention; and (ii) a pharmaceutical composition comprising a compound selected from an anti-diabetic, a hypolipidemic agent, an anti-obesity agent, an anti-hypertensive agent, or a pharmaceutically acceptable salt thereof, in the form of two separate units of the components (i) to (ii).

Likewise, the present invention provides a method as defined above comprising co-administration, e.g., concomitantly or in sequence, of a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof, and at least a second drug substance, said second drug substance preferably being an anti-diabetic, a hypolipidemic agent, an anti-obesity agent or an anti-hypertensive agent, e.g., as indicated above.

Preferably, a compound of the invention is administered to a mammal in need thereof.

Preferably, a compound of the invention is used for the treatment of a disease which responds to a modulation of (especially inappropriate) renin activity.

Preferably, the condition associated with (especially inappropriate) renin activity is selected from hypertension, atherosclerosis, unstable coronary syndrome, congestive heart failure, cardiac hypertrophy, cardiac fibrosis, cardiomyopathy postinfarction, unstable coronary

syndrome, diastolic dysfunction, chronic kidney disease, hepatic fibrosis, complications resulting from diabetes, such as nephropathy, vasculopathy and neuropathy, diseases of the coronary vessels, restenosis following angioplasty, raised intra-ocular pressure, glaucoma, abnormal vascular growth and/or hyperaldosteronism, and/or further cognitive impairment, alzheimers, dementia, anxiety states and cognitive disorders.

Finally, the present invention provides a method or use which comprises administering a compound of formula I in combination with a therapeutically effective amount of an anti-diabetic agent, a hypolipidemic agent, an anti-obesity agent or an anti-hypertensive agent.

Ultimately, the present invention provides a method or use which comprises administering a compound of formula I in the form of a pharmaceutical composition as described herein.

The above-cited properties are demonstrable *in vitro* and *in vivo* tests using advantageously mammals, e.g., mice, rats, rabbits, dogs, monkeys or isolated organs, tissues and preparations thereof. Said compounds can be applied *in vitro* in the form of solutions, e.g., preferably aqueous solutions, and *in vivo* either enterally, parenterally, advantageously intravenously, e.g., as a suspension or in aqueous solution. The concentration level *in vitro* may range between about 10^{-3} molar and 10^{-10} molar concentrations. A therapeutically effective amount *in vivo* may range depending on the route of administration, between about 0.001 and 500 mg/kg, preferably between about 0.1 and 100 mg/kg.

As described above, the compounds of the present invention have enzyme-inhibiting properties. In particular, they inhibit the action of the natural enzyme renin. Renin passes from the kidneys into the blood where it effects the cleavage of angiotensinogen, releasing the decapeptide angiotensin I which is then cleaved in the lungs, the kidneys and other organs to form the octapeptide angiotensin II. The octapeptide increases blood pressure both directly by arterial vasoconstriction and indirectly by liberating from the adrenal glands the sodium-ion-retaining hormone aldosterone, accompanied by an increase in extracellular fluid volume which increase can be attributed to the action of angiotensin II. Inhibitors of the enzymatic activity of renin lead to a reduction in the formation of angiotensin I, and consequently a smaller amount of angiotensin II is produced. The reduced concentration of that active peptide hormone is a direct cause of the hypotensive effect of renin inhibitors.

The action of renin inhibitors may be demonstrated *inter alia* experimentally by means of *in vitro* tests, the reduction in the formation of angiotensin I being measured in various systems (human plasma, purified human renin together with synthetic or natural renin substrate).

Inter alia the following *in vitro* tests may be used:

Recombinant human renin (expressed in Chinese Hamster Ovary cells and purified using standard methods) at 7.5 nM concentration is incubated with test compound at various concentrations for 1 h at RT in 0.1 M Tris-HCl buffer, pH 7.4, containing 0.05 M NaCl, 0.5 mM EDTA and 0.05 % CHAPS. Synthetic peptide substrate Arg-Glu(EDANS)-Ile-His-Pro-Phe-His-Leu-Val-Ile_His_Thr-Lys(DABCYL)-Arg9 is added to a final concentration of 2 µM and increase in fluorescence is recorded at an excitation wave-length of 350 nm and at an emission wave-length of 500 nm in a microplate spectro-fluorimeter. IC50 values are calculated from percentage of inhibition of renin activity as a function of test compound concentration (Fluorescence Resonance Energy Transfer, FRET, assay). Compounds of the formula I, in this assay, preferably can show IC_{50} values in the range from 1 nM to 20 µM.

Alternatively, recombinant human renin (expressed in Chinese Hamster Ovary cells and purified using standard methods) at 0.5 nM concentration is incubated with test compound at various concentrations for 2 h at 37°C in 0.1 M Tris-HCl buffer, pH 7.4, containing 0.05 M NaCl, 0.5 mM EDTA and 0.05 % CHAPS. Synthetic peptide substrate Arg-Glu(EDANS)-Ile-His-Pro-Phe-His-Leu-Val-Ile_His_Thr-Lys(DABCYL)-Arg9 is added to a final concentration of 4 µM and increase in fluorescence is recorded at an excitation wave-length of 340 nm and at an emission wave-length of 485 nm in a microplate spectro-fluorimeter. IC50 values are calculated from percentage of inhibition of renin activity as a function of test compound concentration (Fluorescence Resonance Energy Transfer, FRET, assay). Compounds of the formula I, in this assay, preferably can show IC_{50} values in the range from 1 nM to 20 µM.

In another assay, human plasma spiked with recombinant human renin (expressed in Chinese Hamster Ovary cells and purified using standard methods) at 0.8 nM concentration is incubated with test compound at various concentrations for 2 h at 37°C in 0.1 M Tris/HCl pH 7.4 containing 0.05 M NaCl, 0.5 mM EDTA and 0.025% (w/v) CHAPS. Synthetic peptide substrate Ac-Ile-His-Pro-Phe-His-Leu-Val-Ile-His-Asn-Lys-[DY-505-X5] is added to a final concentration of 2.5 µM. The enzyme reaction is stopped by adding an excess of a blocking inhibitor. The product of the reaction is separated by capillary electrophoresis and quantified by spectrophotometric measurement at 505 nM wave-length. IC50 values are calculated from percentage of inhibition of renin activity as a function of test compound concentration.

Compounds of the formula I, in this assay, preferably can show IC_{50} values in the range from 1 nM to 20 µM.

In another assay, recombinant human renin (expressed in Chinese Hamster Ovary cells and purified using standard methods) at 0.8 nM concentration is incubated with test compound at various concentrations for 2 h at 37°C in 0.1 M Tris/HCl pH 7.4 containing 0.05 M NaCl, 0.5 mM EDTA and 0.025% (w/v) CHAPS. Synthetic peptide substrate Ac-Ile-His-Pro-Phe-His-Leu-Val-Ile-His-Asn-Lys-[DY-505-X5] is added to a final concentration of 2.5 µM. The enzyme reaction is stopped by adding an excess of a blocking inhibitor. The product of the reaction is separated by capillary electrophoresis and quantified by spectrophotometric measurement at 505 nM wave-length. IC50 values are calculated from percentage of inhibition of renin activity as a function of test compound concentration. Compounds of the formula I, in this assay, preferably show IC_{50} values in the range from 1 nM to 20 µM.

In animals deficient in salt, renin inhibitors bring about a reduction in blood pressure. Human renin may differ from the renin of other species. In order to test inhibitors of human renin, primates, e.g.,marmosets (Callithrix jacchus) may be used, because human renin and primate renin are substantially homologous in the enzymatically active region. *Inter alia* the following *in vivo* tests may be used:

Compounds of the formula I can be tested in vivo in primates as described in the literature (see for example by Schnell CR et al. Measurement of blood pressure and heart rate by telemetry in conscious, unrestrained marmosets. Am J Physiol 264 (Heart Circ Physiol 33). 1993: 1509-1516; or Schnell CR et al. Measurement of blood pressure, heart rate, body temperature, ECG and activity by telemetry in conscious, unrestrained marmosets. Proceedings of the fifth FELASA symposium: Welfare and Science. Eds BRIGHTON. 1993.

The following Examples, while representing preferred embodiments of the invention, serve to illustrate the invention without limiting its scope.

Abbreviations:

abs.	Absolute
Ac	acetyl
AcOEt	ethyl acetate

AcOH	acetic acid
aq	aqueous
Bz	benzyl
cc	concentrated
c-hexane	cyclohexane
DIBAL-H	diisobutylaluminium hydride
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DPPA	diphenylphosphoryl azide
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
Ether	diethylether
Et_3N	triethylamine
Et_2O	diethylether
EtOH	ethanol
Flow	flow rate
h	hour(s)
HMPA	hexamethylphosphoroamide
HOBt	1-hydroxybenzotriazole
HPLC	High Performance Liquid Chromatography
iPrOH	isopropanol
L	liter(s)
KHMDS	potassium hexamethyldisilazane
LC-MS	Liquid Chromatography/Mass Spectrometry
LDA	lithium diisopropylamine
Me	methyl
MeI	methyl iodide
MeOH	methanol
MesCl	methanesulfonyl chloride
Min	minute(s)
mL	milliliter
MS	Mass Spectrometry
NMM	4-methylmorpholine
NMR	Nuclear Magnetic Resonance
Pd/C	palladium on charcoal

Ph	phenyl
PyBOP	(benzotriazol-1-yloxy)-tripyrrolidinophosphonium-hexafluorophosphate
RT	room temperature
TBAF	tetra-butylammonium fluoride
TBDMS-Cl	tert-butyldimethylsilyl chloride
TBDMS	tert-butyldimethylsilyl
TBME	tert-Butylmethylether
TEA	triethylamine
TEMPO	2,2,6,6,-tetramethyl-1-piperidinyloxy free radical
TFA	trifluoroacetic acid
THF	tetrahydrofurane
RP	reverse phase
Prep	Preparative
sat.	saturated
TLC	Thin Layer Chromatography
t_r	retention time

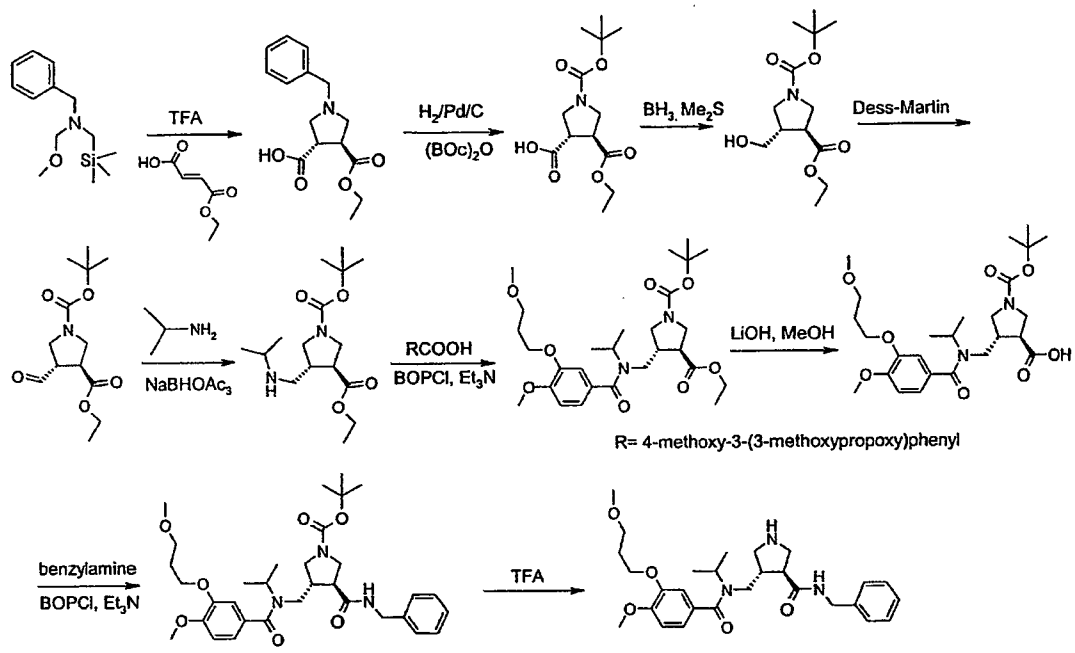
Trademarks

Celite	= Celite® (The Celite Corporation) = filtering aid based on diatomaceous earth
NH_2 Isolute	(= Isolute® NH_2, Isolute® is registered for Argonaut Technologies, Inc.) = ion exchanger with amino groups based on silica gel
Nucleosil	= Nucleosil®, trademark of Machery & Nagel, Düren, FRG for HPLC materials

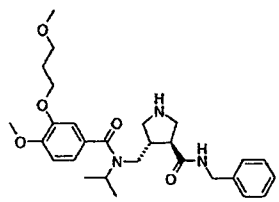
Temperatures are measured in degrees Celsius. Unless otherwise indicated, the reactions take place at RT.

TLC conditions: R_f values for TLC are measured on 5 x 10 cm TLC plates, silica gel F_{254}, Merck, Darmstadt, Germany.

Scheme 1



Example 1: (3S*,4S*)-4-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-3-carboxylic acid benzylamide



To a solution of (3S*,4R*)-3-benzylcarbamoyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (61 mg, 0.098 mmol) in 2 mL CH_2Cl_2, TFA (113 µL, 1.46 mmol) is added. The mixture is stirred at 30°C for 2 h, then overnight at RT, and poured into a saturated solution of $NaHCO_3$. The layers are separated, and the aqueous one is back-extracted twice with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude material is purified by flash chromatography on an NH_2 Isolute SPE Flash column (eluent: CH_2Cl_2:MeOH 100:0 to 95:5) to give the title product. TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0.2. MS (LC-MS): 498 $[M+H]^+$; t_R (HPLC, Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.38 min.

To a solution of the free base in dioxane (2 mL), 4N HCl in dioxane (0.105 mmol, 26 µL) is added, and the resulting solution is lyophilized to afford the corresponding hydrochloride salt as a white powder.

The starting material is prepared as follows:

A. (3S*,4S*)-1-Benzyl-pyrrolidine-3,4-dicarboxylic acid monoethyl ester

To a stirred solution of mono ethyl fumarate (2.85 g, 19.8 mmol) and trifluoroacetic acid (1.98 mmol, 0.15 mL) in methylene chloride (50 mL), N-benzyl-N-(methoxymethyl) trimethylsilyl amine (Aldrich) (9.41 g, 39.6 mmol) is added at 0°C under N_2. The mixture is stirred at 0°C for 30 min and then at RT over 48 h. The crude material is concentrated and purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 85:15 to 85:15 + 2% NH_4OH) to give the title compound. MS (LC-MS): 278.0 $[M+H]^+$. ^{1}H-NMR (CD_3OD, 400 MHz): δ = 1.29 (t, 3H), 3.28 (m, 5H), 3.60 (m, 1H), 4.07 (m, 2H), 4.20 (m, 2H), 7.47 (m, 5H) ppm.

B. (3S*,4S*)-Pyrrolidine-1,3,4-tricarboxylic acid 1-tert-butyl ester 3-ethyl ester

A mixture of (3S*,4S*)-1-benzyl-pyrrolidine-3,4-dicarboxylic acid monoethyl ester (10 g, 36.1 mmol), di-tert-butylcarbonate (7.9 g, 39.6 mmol) and $Pd(OH)_2$/C 20% (1 g, 50% wet) in EtOH (200 mL) is stirred under hydrogen atmosphere for 5 h. The crude material is filtered over a pad of Celite and concentrated. ^{1}H-NMR indicates that the title compound is obtained cleanly. TLC, R_f (AcOEt) = 0.17. MS (LC-MS): 286.1 $[M-H]^-$.

C. (3S*,4S*)-4-Hydroxymethyl-pyrrolidine-1,3-dicarboxylic acid 1-tert-butylester 3-ethyl ester

To a solution of (3S*,4S*)-pyrrolidine-1,3,4-tricarboxylic acid 1-tert-butyl ester 3-ethyl ester (10 g, 34.8 mmol) in THF (180 mL), a solution of borane dimethylsulfide complex (2N in THF, 24.4 mL, 48.7 mmol) is added slowly at -10°C. The mixture is stirred at -10°C for 20 min, then allowed to reach RT and further stirred for 4 h. MeOH is carefully added (exothermic!), and the mixture is concentrated under reduced pressure. MeOH is again added, and the mixture is concentrated. This operation is repeated 3 times, then the mixture is finally taken up into a saturated aqueous solution of $NaHCO_3$ and extracted 3 times with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude material is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH from 100:0 to 95:5) to give the title compound as product. TLC, Rf (AcOEt) = 0.52. MS (LC-MS): 174.1 $[M+H\text{-}Boc]^+$.

D. (3S*,4S*)-4-Formyl-pyrrolidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester

To a well stirred mixture of (3S*,4S*)-4-hydroxymethyl-pyrrolidine-1,3-dicarboxylic acid 1-tert-butylester 3-ethyl ester (3.21 g, 11.74 mmol) and Dess-Martin periodinane (2.63 g, 11.74 mmol) in CH_2Cl_2 (30 mL), slowly wet CH_2Cl_2 (232 µL of water in 10 mL of CH_2Cl_2) is added. The clear solution becomes cloudy toward the end of wet CH_2Cl_2 addition. The mixture is diluted with Et_2O, then concentrated to a few mL of solvent by rotary evaporation. The residue is taken up in Et_2O and then washed with a 1:1 10% $Na_2S_2O_3$ saturated aqueous $NaHCO_3$, followed by H_2O and brine. The aqueous washings are back-extracted with Et_2O, and this organic layer is washed with H_2O and brine. The combined organic layers are dried with Na_2SO_4, filtered and concentrated. The crude mixture is used in the next step without further purification. TLC, R_f (c-hexane/AcOEt 8:2) = 0.2.

E. (3S*,4R*)-4-(Isopropylamino-methyl)-pyrrolidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester

A solution of (3S*,4S*)-4-formyl-pyrrolidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester (2.87 g, 10.56 mmol) and isopropylamine (2.72 mL, 31.68 mmol) in 1,2-dichloroethane (150 mL) is stirred 25 min, before addition of $NaBH(OAc)_3$ (3.12 g, 14.78 mmol) follows. The solution is stirred for 4 h, then diluted with CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The combined organic extracts are dried over Na_2SO_4 and concentrated. The crude material is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 100:0 to 80:20) to give the title product. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.1.

F. (3S*,4R*)-4-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester

A mixture of (3S*,4R*)-4-(isopropylamino-methyl)-pyrrolidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester (2.58 g, 8.2 mmol), 3-(3-methoxy-propoxy)-4-methoxy-benzoic acid (1.93 g, 8.04 mmol), bis(2-oxo-3-oxazolidinyl)phosphinic chloride (2.3 g, 9.02 mmol) and triethylamine (4.57 µL, 32.81 mmol) in CH_2Cl_2 (50 mL) is refluxed for 2 h and then quenched by the addition of aqueous $NaHCO_3$ solution. The organic layer is separated, and the aqueous phase is extracted 3 times with AcOEt. The combined organic extracts are dried (Na_2SO_4), and the solvent is removed *in vacuo*. The crude product is purified by flash chromatography on silica gel (eluent: c-hexane/AcOEt 50:50 to 0:100 and then AcOEt/MeOH 95:5) to give the title product. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.3. t_R (HPLC, C18 column, 10-

100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 5.76 min.

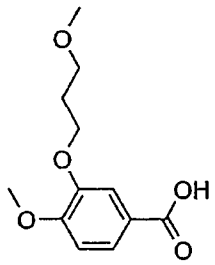
G. (3S*,4R*)-4-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1,3-dicarboxylic acid 1-tert-butyl ester

To a solution of (3S*,4R*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester (1.41 g, 2.63 mmol) in MeOH (25 mL) cooled at 0°C, 662 mg of $LiOH \cdot H_2O$ is added. The reaction mixture is stirred overnight. The mixture is taken up in CH_2Cl_2, an aqueous HCl (5%) solution is added and the resulting mixture is extracted 3 times with CH_2Cl_2, dried over Na_2SO_4, filtered and concentrated. The crude material is used in the next step without purification. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.15. MS (LC-MS): 409.0 $[M-H-Boc]^-$; t_R (HPLC, C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.96 min.

H. (3S*,4R*)-3-Benzylcarbamoyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

To a stirring solution of (3S*,4R*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1,3-dicarboxylic acid 1-tert-butyl ester (70 mg, 0.138 mmol), bis(2-oxo-3-oxazolidinyl)phosphinic chloride (42 mg, 0.166 mmol) and triethylamine (77 µL, 0.552 mmol) in CH_2Cl_2 (3 mL), benzylamine (18 µL, 0.166 mmol) is added. The resulting solution is refluxed for 2 h and then quenched by the addition of aqueous $NaHCO_3$ solution. The organic layer is separated, and the aqueous phase is extracted 3 times with CH_2Cl_2. The combined organic extracts are dried (Na_2SO_4), and the solvent is removed *in vacuo*. The crude material is purified by preparative HPLC (C18-ODB-AQ, 5 µm, 20x50 mm, YMC, eluent: CH_3CN/H_2O + 0.1 % HCOOH flow: 20 mL/min). The HPLC fractions are collected and lyophilized to afford the title product. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.2. MS (LC-MS): 598.0 $[M+H]^+$; t_R (HPLC, C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 5.60 min.

4-Methoxy-3-(3-methoxy-propoxy)-benzoic acid



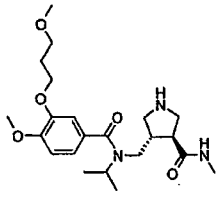
a. 4-Methoxy-3-(3-methoxy-propoxy)-benzoic acid methyl ester

A solution of methyl-3-hydroxy-4-methoxybenzoate (Aldrich) (89.3 g, 0.49 mol), K_2CO_3 (100.5 g, 0.727 mol) and 1-bromo-3-methoxy-propane (80 g, 0.523 mol) in CH_3CN (1100 mL) is refluxed for 6 h. After completion of the reaction, the mixture is cooled to RT and concentrated under reduced pressure. The residue is taken up into AcOEt (500 mL) and washed with water. The aqueous layer is back-extracted twice with AcOEt, and the combined organic extracts are dried over $MgSO_4$, filtered and concentrated to afford the title compound which is further used in the next step without purification. t_R (HPLC, CC 70/4 Nucleosil 3 C18HD column, 20 to 100% CH_3CN in H_2O in 2, then 4 min with 100% CH_3CN, CH_3CN and H_2O with 0.1% TFA, flow: 1.5 mL/min): 3.07 min.

b. 4-Methoxy-3-(3-methoxy-propoxy)-benzoic acid

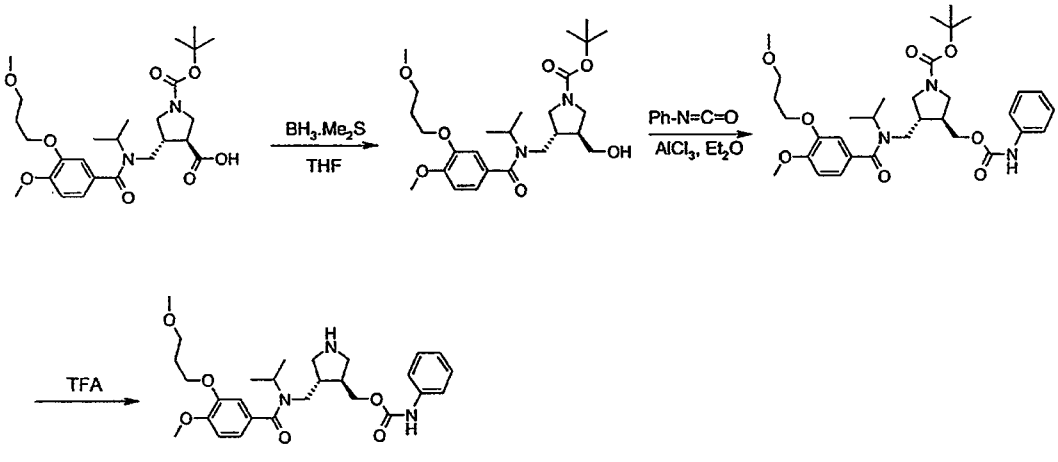
A solution of 4-methoxy-3-(3-methoxy-propoxy)-benzoic acid methyl ester (140 g, 0.55 mol) and NaOH (1N, 825 mL, 0.825 mol) in MeOH (840 mL) is stirred at RT for 18 h. After completion, the solvent is removed under reduced pressure, and the residue is diluted with water (200 mL) and extracted twice with AcOEt (250 mL). The aqueous layer is acidified by addition of aqueous HCl (2N, 470 mL) and extracted 3 times with AcOEt (1 L). The combined organic extracts are washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude material is purified by crystallization in AcOEt to give the title compound. MS (LC-MS): 239.1 $[M-H]^-$; t_R (HPLC, CC 70/4 Nucleosil 3 C18HD column, 20 to 100% CH_3CN in H_2O in 2, then 4 min with 100% CH_3CN, CH_3CN and H_2O with 0.1% TFA , flow: 1.5 mL/min): 2.43 min.

Example 2: (3S*,4S*)-4-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-3-carboxylic acid methylamide

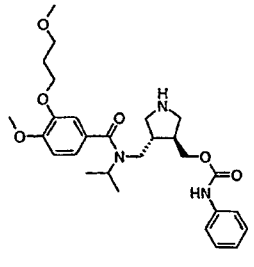


The title compound is prepared analogously as described for the title compound Example 1, starting from (3S*,4R*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1,3-dicarboxylic acid 1-tert-butyl ester and methylamine. MS (LC-MS): 422.1 $[MH]^+$; t_R (HPLC, nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, flow: 1.5 ml/min): 3.83 min.

Scheme 2



Example 3: Phenyl-carbamic acid (3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl ester



To a solution of (3R*,4S*)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-phenyl carbamoyloxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (68 mg,

0.11 mmol) in 2 mL CH_2Cl_2, TFA (128 µL, 1.66 mmol) is added. The mixture is stirred at 30°C for 2 h, then overnight at RT, and poured into a saturated solution of $NaHCO_3$. The layers are separated, and the aqueous one is back-extracted twice with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude material is purified by flash chromatography on Isolute SPE Flash NH_2 column (eluent: CH_2Cl_2/MeOH 100:0 to 97:3) to give the title product. MS (LC-MS): 514.0 $[M+H]^+$; t_R (HPLC, Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.52 min.

To a solution of the free base in dioxane (2 mL), 4N HCl in dioxane (0.099 mmol, 25 µL) is added, and the resulting solution is lyophilized to afford the corresponding hydrochloride salt as a white powder.

The starting material is prepared as follows:

A. (3S*,4R*)-3-Hydroxymethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

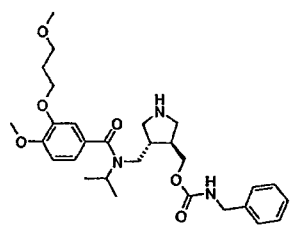
To a solution of (3S*,4R*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1,3-dicarboxylic acid 1-tert-butyl ester (1.29 g, 2.54 mmol) (Example 1 G) in THF (25 mL), a solution of borane dimethylsulfide complex (2M in THF, 2.80 mL, 5.58 mmol) is slowly added at -10°C. The mixture is stirred for 20 min at -10°C, then allowed to reach RT and further stirred overnight. MeOH is carefully added (exothermic!), and the mixture is concentrated under reduced pressure. MeOH is again added, and the mixture is concentrated. This operation is repeated 3 times, and the mixture is finally taken up into a saturated aqueous solution of $NaHCO_3$ and extracted 3 times with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude material is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH from 100:0 to 95:5) to give the desired product. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.3. MS (LC-MS): 395.1 [M+H-Boc]$^+$; t_R (HPLC, C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 5.01 min.

B. (3R*,4S*)-3-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-phenyl carbamoyloxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

Phenyl isocyanate (44 µL, 0.404 mmol) followed by $AlCl_3$ (27 mg, 0.202 mmol) are added to a solution of (3S*,4R*)-3-hydroxymethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-

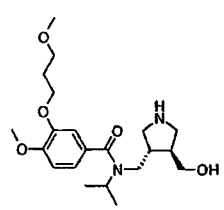
benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (100 mg, 0.202 mmol) in Et_2O (6 mL). The resulting mixture is stirred at RT overnight. For workup, a sat. solution of $NaHCO_3$ is added and the mixture is extracted with ethyl acetate. The combined extracts are dried (Na_2SO_4) and the solvent is evaporated. The crude product is purified by flash chromatography on silica gel (eluent: c-hexane/AcOEt 80:20 to 0:100) to give the title product. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.5. MS (LC-MS): 514.0 $[M+H\text{-}Boc]^+$; t_R (HPLC, C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.91 min.

Example 4 : Benzyl-carbamic acid (3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl ester



The title compound is prepared analogously as described in Example 3 from (3S*,4R*)-3-hydroxymethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester and benzylisocyanate. MS (LC-MS): 528.3 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.52 min.

Example 5: N-((3S*,4S*)-4-Hydroxymethyl-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

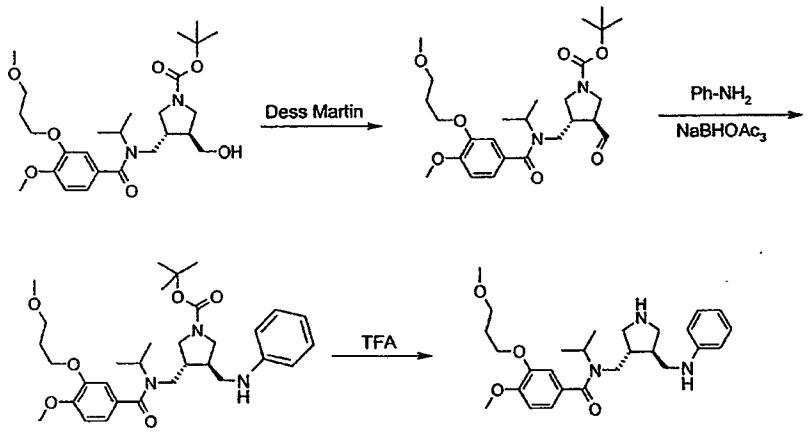


To a solution of (3S*,4R*)-3-hydroxymethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (85 mg, 0.172 mmol) in 2 mL CH_2Cl_2, TFA (85 µL, 2.23 mmol) is added. The mixture is stirred 4.5 h at RT, and poured into a saturated solution of $NaHCO_3$. The layers are separated, and the aqueous one

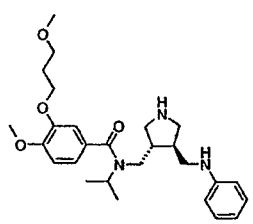
is back-extracted twice with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude material is purified by flash chromatography on Isolute SPE Flash NH_2 column (eluent: CH_2Cl_2/MeOH 100:0 to 99:1) to give the title product. MS (LC-MS): 395.1 $[M+H]^+$; t_R (HPLC, Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 3.75 min.

To a solution of the free base in dioxane (2 mL), 4N HCl in dioxane (0.009 mmol, 2.2 µL) is added, and the resulting solution is lyophilized to afford the corresponding hydrochloride salt as a white powder.

Scheme 3



Example 6: N-Isopropyl-4-methoxy-3-(3-methoxy-propoxy)-N-((3S*,4S*)-4-phenylamino methyl-pyrrolidin-3-ylmethyl)-benzamide



To a solution of (3R*,4R*)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-phenylaminomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (65 mg, 0.12 mmol) in 2 mL CH_2Cl_2, TFA (139 µL, 1.8 mmol) is added. The mixture is stirred 2 h at RT, and poured into a saturated solution of $NaHCO_3$. The layers are separated, and the aqueous

one is back-extracted twice with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude material is purified by flash chromatography on an Isolute SPE Flash NH_2 column (eluent: CH_2Cl_2/MeOH 100:0 to 97:3) to give the title product. TLC, R_f (SiO_2-NH_2, CH_2Cl_2/MeOH 95:5) = 0.6. MS (LC-MS): 470.0 $[M+H]^+$; t_R (HPLC, Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 3.37 min.

To a solution of the free base in dioxane (2 mL), (0.242 mmol, 60 µL) of 4N HCl in dioxane is added, and the resulting solution is lyophilized to afford the corresponding dihydrochloride salt as a white powder.

The starting material is prepared as follows:

A. (3S*,4R*)-3-Formyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

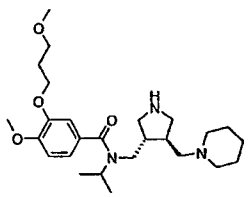
To a well-stirred mixture of (3S*,4R*)-3-hydroxymethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (600 mg, 1.21 mmol) and Dess-Martin periodinane (272 mg, 1.21 mmol) in CH_2Cl_2 (10 mL), slowly wet CH_2Cl_2 (24 µL of water in 2 mL of CH_2Cl_2) is added. The clear solution becomes cloudy towards the end of wet CH_2Cl_2 addition. The mixture is diluted with Et_2O and concentrated to a few mL of solvent by rotary evaporation. The residue is taken up in Et_2O, and washed with a 1:1 10% $Na_2S_2O_3$ / saturated aqueous solution of $NaHCO_3$, followed by H_2O and brine. The aqueous washings are back-extracted with Et_2O, and this organic layer is washed with H_2O and brine. The combined organic layers are dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material is used without further purification in the next step. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.3. t_R (HPLC, Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.16 min.

B. (3R*,4R*)-3-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-phenylaminomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

A solution of (3S*,4R*)-3-formyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (100 mg, 0.20 mmol) and aniline (26 µL, 0.28 mmol) in 1,2-dichloroethane (5 mL) is stirred 25 min, before the addition of $NaBH(OAc)_3$ (60 mg, 0.28 mmol) follows. The solution is stirred overnight at RT, then diluted

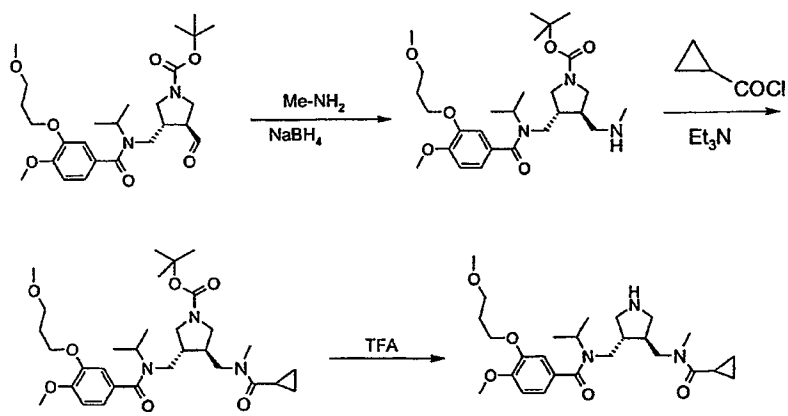
with CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The combined organic extracts are dried over Na_2SO_4 and concentrated. The crude material is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 100:0 to 97:3) to give the title product. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.25. MS (LC-MS): 570.0 $[M+H]^+$; t_R (HPLC, nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.31 min.

Example 7 : N-Isopropyl-4-methoxy-3-(3-methoxy-propoxy)-N-((3S*,4S*)-4-piperidin-1-ylmethyl-pyrrolidin-3-ylmethyl)-benzamide

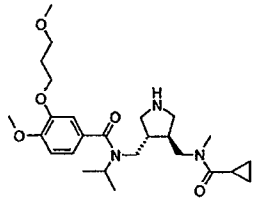


The title compound is prepared analogously as described in Example 5 from (3S*,4R*)-3-formyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester and piperidine. MS (LC-MS): 462.1 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 3.74 min.

Scheme 4



Example 8: N-{(3S*,4S*)-4-[(Cyclopropanecarbonyl-methyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide



To a solution of (3R*,4R*)-3-[(cyclopropanecarbonyl-methyl-amino)-methyl]-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (154 mg, 0.267 mmol) in 3 mL CH_2Cl_2, TFA (309 µL, 4.01 mmol) is added. The mixture is stirred 4 h at RT, and poured into a saturated solution of $NaHCO_3$. The layers are separated, and the aqueous one is back-extracted twice with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude material is purified by flash chromatography on Isolute SPE Flash NH_2 column (eluent: CH_2Cl_2 /MeOH 100:0 to 95:5) to give the title product. TLC, R_f (SiO_2-NH_2, CH_2Cl_2/MeOH 95:5) = 0.1. MS (LC-MS): 476.1 $[M+H]^+$; t_R (HPLC, Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.10 min.

To a solution of the free base in dioxane (2 mL), 4N HCl in dioxane (0.198 mmol, 50 µL) is added, and the resulting solution is lyophilized to afford the corresponding dihydrochloride salt as a white powder.

The starting material is prepared as follows:

A. (3R*,4R*)-3-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-methylaminomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

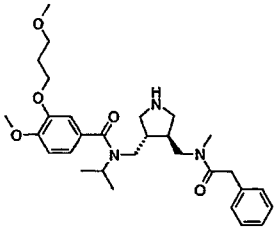
To a solution of (3S*,4R*)-3-formyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (150 mg, 0.304 mmol) and magnesium sulfate (92 mg, 0.373 mmol) in THF (4 mL), methylamine (1.52 mL, 3.044 mmol, 2M in THF) is added. The solution is stirred at RT overnight under nitrogen atmosphere and $NaBH_4$ (23 mg, 0.608 mmol) is added. The resulting mixture is stirred for 1 h and the excess reducing agent quenched with water, CH_2Cl_2 is added and the reaction mixture is poured into an aqueous saturated solution of $NaHCO_3$. The organic layer is separated and the aqueous phase extracted twice with CH_2Cl_2, dried over Na_2SO_4, filtered, and

concentrated in vacuo. The crude material is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 100:0 to 95:5 +1% NH_4OH) to give the title product. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.05. MS (LC-MS) $[M-H]^+$ =508.1. t_R (HPLC, Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 4.53 min.

B. (3R*,4R*)-3-[(Cyclopropanecarbonyl-methyl-amino)-methyl]-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (3R*,4R*)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-methylaminomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (134 mg, 0.264 mmol) in CH_2Cl_2 (2 mL), cyclopropanecarbonyl chloride (29 µL, 0.317 mmol) and triethylamine (44 µL, 0.317 mmol) are added under N_2 atmosphere. The mixture is stirred overnight at RT, diluted with CH_2Cl_2 and poured into an aqueous saturated solution of $NaHCO_3$. The organic layer is separated, and the aqueous one is extracted twice with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude product is used in the next step without purification. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.2. MS (LC-MS): 476.1 $[M+H\text{-}Boc]^+$. t_R (HPLC, Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.42 min.

Example 9: N-Isopropyl-4-methoxy-3-(3-methoxy-propoxy)-N-{(3S,4S)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-benzamide



To a solution of (3R,4R)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester (0.36 g, 0.575 mmol) in 12 mL CH_2Cl_2, TFA (0.664 mL, 8.62 mmol) is added. The mixture is stirred 2 h at 30°C, and poured into a saturated solution of $NaHCO_3$. The layers are separated, and the aqueous one is back-extracted twice with CH_2Cl_2. The combined organic

extracts are dried over Na_2SO_4, filtered and concentrated. To a solution of the free base in dioxane (3 mL), 4N HCl in dioxane (0.144 mL) is added, and the resulting solution is lyophilized to afford the corresponding hydrochloride salt. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.1. MS (LC-MS): 526.1 [M+H]+; t_R (Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.41 min.

The starting material is prepared as follows:

A. (3R,4R)-3-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester

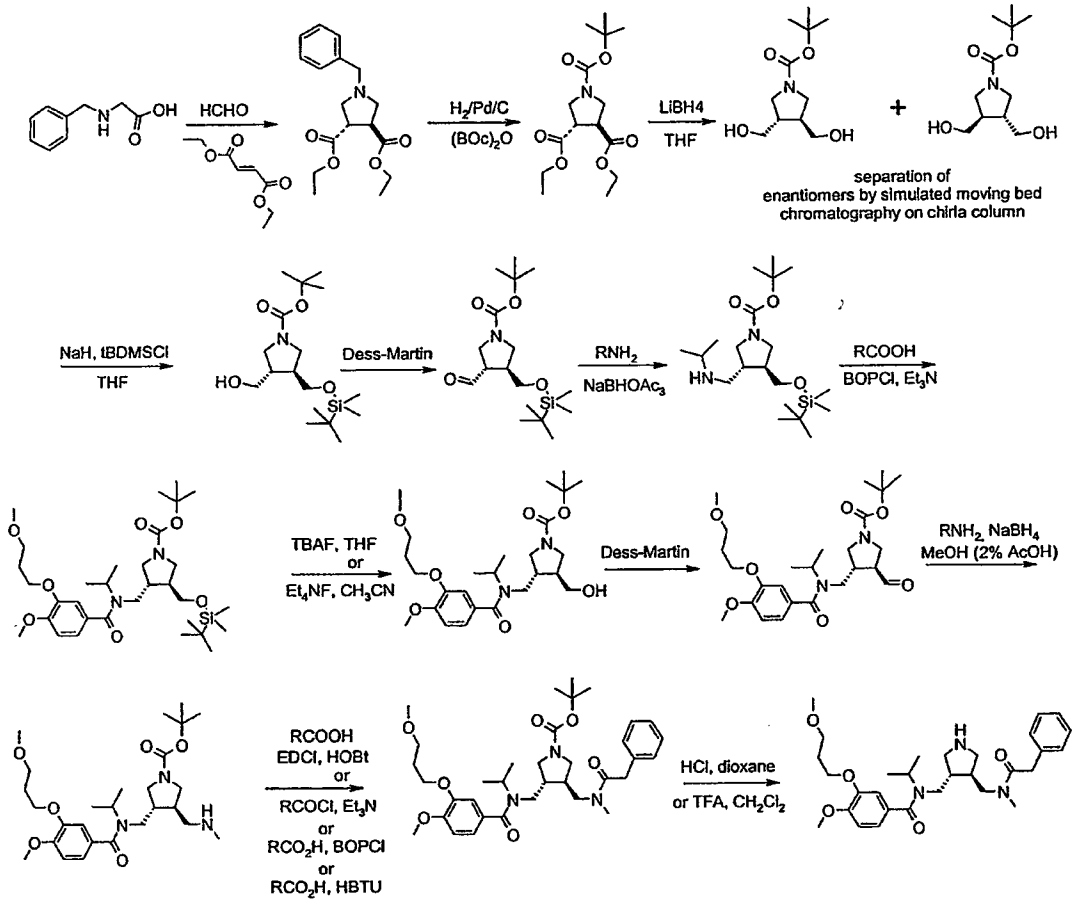
Racemic (3R*,4R*)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester is separated into the single enantiomers by preparative chiral HPLC on a Chiralpak AD-H column (4.6x250 mm, 5 µM particle size; flow rate 1 mL /min, UV = 210 nM, injection = 1.7 g in 5 mL ethanol and using ethanol as the eluent to give the enantiomerically pure title compound: t_R (HPLC, Chiralpak AD-H, HPLC 250X4.6 mm, ethanol, flow: 0.5 ml/min): 26.46 min; and (3S,4S)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester: t_R (HPLC, Chiralpak AD-H, HPLC 250X4.6 mm, ethanol, flow: 0.5 ml/min): 13.53 min.

B. (3R*,4R*)-3-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-methylaminomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound is prepared from (3R*,4R*)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-methylaminomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (79 mg, 0.165 mmol) and phenylacethyl chloride according to Example 8, reaction step B. R_f (CH_2Cl_2/MeOH 95:5) = 0.4. MS (LC-MS): 526.1 [M+H]+; t_R (Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.71 min.

Alternatively, the starting material (3R,4R)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester is prepared according to scheme 5 as follows:

Scheme 5



A. (3S*,4S*)-1-Benzyl-pyrrolidine-3,4-dicarboxylic acid diethyl ester

A mixture of N-benzylglycine (51.3 g, 310.55 mmol), diethylfumarate (51.85 mL, 316.76 mmol) and paraformaldehyde powder (10.25 g, 341.6 mmol) in toluene (500 mL) is heated at reflux for 2 h, while collecting water using a dean-stark apparatus. The solvent is concentrated and the mixture purified by distillation under vacuum (~50 mbar), the desired title compound distilling at 80-85°C. TLC, R_f (CH_2Cl_2/acetone 95:5) =0.56. MS (LC-MS): 306.2 $[M+H]^+$; t_R (HPLC, RP8 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/2.5min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.35 min.

B. (3S*,4S*)-Pyrrolidine-1,3,4-tricarboxylic acid 1-tert-butyl ester 3,4-diethyl ester

A mixture of (3S*,4S*)-1-benzyl-pyrrolidine-3,4-dicarboxylic acid diethyl ester (82.8 g, 271.14 mmol), di-tert-butylcarbonate (88.76 g, 406.71 mmol) and Pd/C 10% (8 g) in EtOH (1.5 L) is stirred under hydrogen atmosphere. The crude material is filtered over a pad of Celite and concentrated. The crude material is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/acetone 100:0 to 95:5). TLC, R_f (CH_2Cl_2/acetone 95:5) = 0.51. MS (LC-MS): 216.2 $[M+H\text{-}Boc]^+$.

C. (3S*,4S*)-3,4-Bis-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

To a ice-cooled solution of (3S*,4S*)-pyrrolidine-1,3,4-tricarboxylic acid 1-tert-butyl ester 3,4-diethyl ester (36 g, 114.15 mmol) in THF (1 L), is added dropwise a solution of $LiBH_4$ (228.3 mmol) in THF (250 mL). The reaction mixture is stirred overnight at room temperature and quenched with an aqueous solution of NaOH 2N (400 mL). Ether is added, the layers are separated and the aqueous one back extracted twice with ether. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated to give the title compound which is used without further purification in the next step. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.14. MS (LC-MS): 232.2 $[M+H]^+$; t_R (HPLC, C18 column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 3.37 min.

(3S,4S)-3,4-Bis-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester and (3R,4R)-3,4-Bis-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

The two enantiomers are separated via chiral preparative HPLC using simulated moving bed chromatography (SMB) "UOP SORBEX Prep." Technology with 16 columns "Princeton Chromatography Inc." (7.5 x 2.12 cm), stationary phase: Chiralpak AD Prep. 20 µm, (eluent: hexane/EtOH/MeOH 90:5:5).

(3S,4S)-3,4-Bis-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester: t_R (Chiralpak AD-H, 250 x 4.6 mm, flow rate 1 mL /min) (eluent: hexane/EtOH 90:10): 6.4 min. $[\alpha]_D$ = -11.1 (c = 1.795, $CHCl_3$).

(3R,4R)-3,4-Bis-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester: t_R (Chiralpak AD-H, 250 x 4.6 mm, flow rate 1 mL :min) (eluent: hexane/EtOH 90:10): 8.58 min. $[\alpha]_D$ = +10.2 (c = 1.795, $CHCl_3$).

D. (3S,4S)-3-(tert-Butyl-dimethyl-silanyloxymethyl)-4-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

To a suspension of sodium hydride (60 % in oil, 0.996 g, 24.9 mmol) (previously washed with pentane) in THF (40 mL) is added dropwise under a nitrogen atmosphere a solution of (3S,4S)-3,4-bis-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (4.8 g, 20.75 mmol) in THF (40 mL) at 0°C. The mixture is stirred for 1.5 h at 0°C before the dropwise addition of a solution of tert-butyl(chloro)dimethylsilane (3.44 g, 22.83 mmol) in THF (40 mL). The resulting mixture is further stirred 1 h at 0°C and 1 h at RT, then poured into an aqueous solution of $NaHCO_3$ (5%) (150 mL) and extracted 3 times with Et_2O. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude material is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 99:1 to 93:7). TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.33. MS (LC-MS): 346.2 $[M+H]^+$.

E. (3S,4S)-3-(tert-Butyl-dimethyl-silanyloxymethyl)-4-formyl-pyrrolidine-1-carboxylic acid tert-butyl ester

To a well stirred mixture of (3S,4S)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (8.2 g, 23.73 mmol) and Dess-Martin periodinane (10.06 g, 23.73 mmol) in CH_2Cl_2 (60 mL), slowly wet CH_2Cl_2 (0.47 mL of water in 60 mL of CH_2Cl_2) is added. The clear solution becomes cloudy toward the end of wet CH_2Cl_2 addition and is further stirred over-night. Then concentrated to a few mL of solvent by rotary evaporation and taken up in Et_2O. A solution of 1:1 10% $Na_2S_2O_3$/saturated aqueous $NaHCO_3$ is added. The layers are separated and the organic extract is washed successively with H_2O and brine. The aqueous washings are back-extracted with Et_2O, and this organic layer is washed with H_2O and brine. The combined organic layers are dried with Na_2SO_4, filtered and concentrated. The crude mixture is used in the next step without further purification. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.42. MS (LC-MS): 244.2 $[M+H\text{-}Boc]^+$; t_R (HPLC, C18 column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 6.45 min.

F. (3S,4R)-3-(tert-Butyl-dimethyl-silanyloxymethyl)-4-(isopropylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

A solution of (3S,4S)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-formyl-pyrrolidine-1-carboxylic acid tert-butyl ester (7.7 g, 22.41 mmol) and isopropylamine (5.78 mL, 67.24 mmol) in 1,2-dichloroethane (200 mL) is stirred 25 min before the addition of $NaBH(OAc)_3$ (11.88 g, 56.03 mmol). The solution is stirred for 5 h, then diluted with CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The aqueous layer is back extracted twice

I. (3S,4R)-3-Formyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound is prepared analogously as described for the title compound under E in Scheme 5 from (3S,4R)-3-hydroxymethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.3. t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.16 min.

J. (3R,4R)-3-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-methylaminomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (3S,4R)-3-formyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (2.7 g, 5.48 mmol) in MeOH (containing 2% AcOH, 25 mL), methylamine (13.7 mL, 27.41 mmol, 2M in MeOH) is added. The solution is stirred at RT for 1 h under nitrogen atmosphere and cooled to 10°C, before the careful addition of $NaBH_4$ (0.415 g, 10.96 mmol) (exothermic !!). The resulting mixture is allowed to reach RT and stirred for 1.5 h. The excess reducing agent is quenched with water, AcOEt is added and the reaction mixture is poured into an aqueous saturated solution of $NaHCO_3$. The organic layer is separated and the aqueous layer extracted twice with AcOEt, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material is used in the next step without further purification. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.05. MS (LC-MS) [M+H]+ = 508.1. t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 4.53 min.

K. (3R,4R)-3-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (3R,4R)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-methylaminomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (2 g, 3.35 mmol) in CH_2Cl_2 (25 mL), phenylacetyl chloride (0.53 mL, 4.02 mmol) and triethylamine (0.56 mL, 4.02 mmol) are added under N_2 atmosphere at 0°C. The mixture is stirred 30 min at 0°C, then allowed to reach RT and further stirred for 1 h. The reaction mixture is diluted with CH_2Cl_2 and poured into an aqueous saturated solution of $NaHCO_3$. The organic layer is separated, and the aqueous one is extracted twice with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude product is purified by

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flash chromatography on silica gel (eluent: c-hexane/AcOEt 20:80 to 0:100) to give the title compound. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.4. MS (LC-MS): 526 $[M\text{-}Boc+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.71 min.

In a similar fashion as described above for Example 9/reaction step J,

(3R*,4R*)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-methylaminomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

is prepared from racemic (3S*,4R*)-3-formyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester by reductive amination with methylamine in presence of $NaBH_4$: TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.05. MS (LC-MS) [M+H]+ = 508.1. t_R (HPLC, Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 4.53 min.

A. (3S*,4S*)-3-(tert-Butyl-dimethyl-silanyloxymethyl)-4-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound is prepared in a similar manner as described for Example 9/reaction step D, from (3S*,4S*)-3,4-bis-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (25.0 g, 108 mmol), tert-butyl(chloro)dimethylsilane (17.9 g, 119 mmol) and NaH (3.11 g, 130 mmol; 55-65% dispersion in oil) in THF (0.6 L) as a yellowish oil. MS: 346.2 $[M+H]^+$.

B. (3S*,4S*)-3-(tert-Butyl-dimethyl-silanyloxymethyl)-4-formyl-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound is prepared in a similar manner as described for Example 9/reaction step E, from (3S*,4S*)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (10.4 g, 58.9 mmol) and Dess-Martin periodinane (25.0 g, 58.9 mmol) in CH_2Cl_2 (150 mL), slowly wet CH_2Cl_2 (1.17 mL of water in 150 mL of CH_2Cl_2) as colorless oil. MS: 244.2 $[M+H\text{-}Boc]^+$. t_R (HPLC, C18 column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 6.46 min.

C. (3S*,4R*)-3-(tert-Butyl-dimethyl-silanyloxymethyl)-4-(isopropylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound is prepared in a similar manner as described for Example 9/reaction step F, from (3S*,4S*)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-formyl-pyrrolidine-1-carboxylic acid tert-butyl ester (19.3 g, 56.1 mmol), isopropylamine (14.5 mL, 168 mmol) and $NaBH(OAc)_3$ (29.7 g, 140 mmol) in 1,2-dichloroethane (0.5 L) as a yellowish oil. MS: 387.2 $[M+H]^+$. t_R (HPLC, C18 column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 5.34 min.

D. (3S*,4R*)-3-(tert-Butyl-dimethyl-silanyloxymethyl)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound is prepared in a similar manner as described for Example 9/reaction step G, from ((3S*,4R*)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-(isopropylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (22.9 g, 59.1 mmol), 3-(3-methoxy-propoxy)-4-methoxy-benzoic acid (15.6 g, 65.1 mmol), bis(2-oxo-3-oxazolidinyl)phosphinic chloride (16.6 g, 65.1 mmol) and triethylamine (19.6 mL, 237 mmol) in CH_2Cl_2 (0.6 L) as a yellowish oil. MS: 609.4 $[M+H]^+$; t_R (HPLC, C18 column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 7.06 min.

E. (3S*,4R*)-3-Hydroxymethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

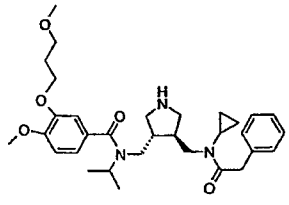
The title compound is prepared in a similar manner as described for Example 9/reaction step H, from (3S*,4R*)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (25.0 g, 41.1 mmol) and tetrabutylammonium fluoride trihydrate (19.4 g, 61.6 mmol) in THF (150 mL) as a colorless oil. MS: 495.2 [M+H]+; t_R (HPLC, C18 column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/1.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.84 min.

F. (3S*,4R*)-3-Formyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound is prepared in a similar manner as described for Example 9/reaction step I, from (3S*,4R*)-3-hydroxymethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (4.9 g, 9.95 mmol) and Dess-Martin periodinane (4.22 g, 9.95 mmol) in CH_2Cl_2 (30 mL), slowly wet CH_2Cl_2 (0.20 mL of

water in 30 mL of CH_2Cl_2) as colorless oil. MS: 437.2 [M+H-BOC]+. t_R (HPLC, Nucleosil C18 column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/1.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 4.99 min.

Example 10 : N-{(3S,4S)-4-[(Cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide



A solution of (3R,4R)-3-[(cyclopropyl-phenylacetyl-amino)-methyl]-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.32 g, 0.48 mmol) in a 4N HCl solution in dioxane (2.0 mL) is stirred at room temperature overnight. The reaction mixture is then freeze-dried to afford the corresponding hydrochloride salt as white solid. MS: 552.2 [M]+; t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/1.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.72 min.

The starting material is prepared as follows:

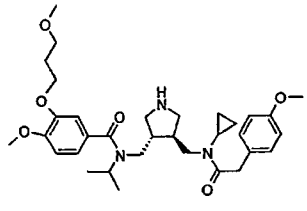
A. (3R,4R)-3-Cyclopropylaminomethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

A solution of (3S,4R)-3-formyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (7.45 g, 15.1 mmol; Example 9 / reaction step I) and cycloproyplamine (5.30 mL, 75.6 mmol) in MeOH (containing 2% AcOH, 90 mL) is stirred for 1 h at room temperature, followed by portionwise addition of NaBH4 (1.14 g, 30.2 mmol). After stirring for 1 h, the reaction mixture is concentrated to one third of its volume, water and a saturated NaHCO3 solution are added and the aqueous layer is extracted with AcOEt. The combined organics are dried (Na2SO4) and evaporated to dryness to afford the title compound as colorless oil. The crude material is used in the next step without further purification. MS (LC-MS) [M+H]+ = 534.2. t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/1.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.79 min.

B. (3R,4R)-3-[(Cyclopropyl-phenylacetyl-amino)-methyl]-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (3R,4R)-3-cyclopropylaminomethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.30 g, 0.56 mmol) in CH2Cl2 (6 mL) are subsequently added Et3N (0.094 mL, 0.67 mmol), 1-hydroxy-benzotriazol hydrate (0.09 g, 0.67 mmol), N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide hydrochloride (0.129 g, 0.67 mmol) and phenylacetic acid (0.09 g, 0.67 mmol), followed by stirring overnight. The reaction mixture is diluted with CH2Cl2 and then washed with 1N HCl (5 mL), saturated aqueous NaHCO3 and brine, the organic layer is dried over MgSO4 and concentrated. Purification by flash chromatography (eluent: hexane/AcOEt 25:75, then AcOEt 100%) gives the title compound as colorless oil. MS (LC-MS): 652.4 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/1.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 5.80 min.

Example 11 : N-[(3S*,4S*)-4-({Cyclopropyl-[2-(4-methoxy-phenyl)-acetyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide



To a solution of (3R*,4R*)-3-({cyclopropyl-[2-(4-methoxy-phenyl)-acetyl]-amino}-methyl)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.17 g, 0.26 mmol) in dioxane (1 mL), 4N HCl in dioxane (0.647 mL) is added, and the resulting solution is lyophilized to afford the corresponding hydrochloride salt. TLC, R_f (CH_2Cl_2/MeOH 9:1 + 10 % NH_4OH) = 0.2. MS (LC-MS): 582.4 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.06 min.

The starting material is prepared as follows:

A. (3R*,4R*)-3-Cyclopropylaminomethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound is prepared analogously as described for the title compound under J in Example 9 from (3S*,4R*)-3-formyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester and cyclopropylamine. TLC, R_f (CH_2Cl_2/MeOH 9:1 + 10 % NH_4OH) = 0.48. MS (LC-MS): 534.4 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.53 min.

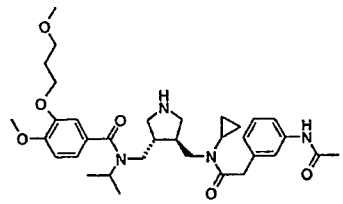
B. (3R*,4R*)-3-({cyclopropyl-[2-(4-methoxy-phenyl)-acetyl]-amino}-methyl)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of 4-methoxyphenylacetic acid (0.075 g, 0.45 mmol) in CH_2Cl_2 (3 mL), are added triethylamine (0.063 mL, 0.45 mmol), 1-hydroxy-benzotriazol hydrate (0.061 g, 0.45 mmol) and N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide hydrochloride (EDC) (0.086 g, 0.45 mmol) followed by (3R*,4R*)-3-cyclopropylaminomethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.2 g, 0.375 mmol). The resulting mixture is stirred for 2 days at RT, then diluted with CH_2Cl_2 and poured into an aqueous saturated solution of $NaHCO_3$. The organic layer is separated, and the aqueous one is extracted twice with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude product is purified by flash chromatography on silica gel (eluent: c-hexane/AcOEt 50:50 to 0:100) to give the title compound. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.35. MS (LC-MS): 682.4 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 5.77 min.

Alternatively, the coupling reaction is performed in a similar manner as described above using 1.1 equivalents of HOBt, EDC, NEt_3 and a mixture of DMF/THF 1:1.

Example 12 : N-[(3S*,4S*)-4-({[2-(3-Acetylamino-phenyl)-acetyl]-cyclopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

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To a solution of (3R*,4R*)-3-({[2-(3-acetylamino-phenyl)-acetyl]-cyclopropyl-amino}-methyl)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.31 g, 0.44 mmol) in dioxane (15 mL), 4N HCl in dioxane (6 mL) is added, the resulting solution is stirred at RT for 8h and then lyophilized to afford the corresponding hydrochloride salt. MS (LC-MS): 609.1 $[M+H]^+$; t_R (HPLC, Macherey Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 5.03 min.

The starting material is prepared as follows:

A. (3R*,4R*)-3-({Cyclopropyl-[2-(3-nitro-phenyl)-acetyl]-amino}-methyl)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

At 0°C HBTU (426 mg, 1.12 mmol) is added to a solution of 3-nitrophenylacetic acid (187 mg, 1.03 mmol) in CH_3CN (10 mL) and the resulting solution is stirred for 10 min. Then a solution of (3R*,4R*)-3-cyclopropylaminomethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.2 g, 0.375 mmol). (500 mg, 0.94 mmol) and triethylamine (1.04 mL, 7.5 mmol) in CH_3CN (10 mL) is added at 0°C and the reaction mixture is stirred at RT for another 2 h. For workup a sat. solution of $NaHCO_3$ is added and the mixture is extracted with ethyl acetate. Washing of the combined extracts with brine, drying (Na_2SO_4), filtration and evaporation of the solvent affords the crude product which is purified by flash chromatography on silica gel (eluent: CH_2Cl_2 to CH_2Cl_2/MeOH 9:1) to give the title compound. MS (LC-MS): 597.0 $[M+H-Boc]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 6.47 min.

B. (3R*,4R*)-3-({[2-(3-Amino-phenyl)-acetyl]-cyclopropyl-amino}-methyl)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

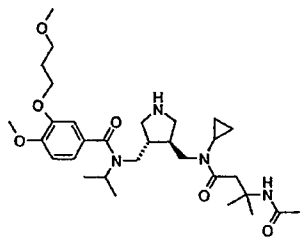
At RT H_2 is passed through a suspension of (3R*,4R*)-3-({cyclopropyl-[2-(3-nitro-phenyl)-acetyl]-amino}-methyl)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (660 mg, 0.95 mmol) and Raney-Ni (100 mg) for several hours. After completion of the reaction the mixture is filtered over Celite and the solvent is evaporated to give the title compound which is used without further purification. MS (LC-MS): 667.0 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 5.33 min.

C. (3R*,4R*)-3-({[2-(3-Acetylamino-phenyl)-acetyl]-cyclopropyl-amino}-methyl)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

Triethylamine (67 µL, 0.48 mmol), DMAP (0.4 mg, 0.003 mmol) and acetic anhydride (46 µL, 0.48 mmol) are added to a solution of (3R*,4R*)-3-({[2-(3-amino-phenyl)-acetyl]-cyclopropyl-amino}-methyl)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (215 mg, 0.32 mmol) in THF (20 mL). The reaction mixture is stirred at RT for 16 h before water is added for workup. Extraction with ethyl acetate, drying of the combined extracts (Na_2SO_4), filtration and evaporation of the solvent affords the crude product which is purified by flash chromatography on silica gel (eluent: CH_2Cl_2 to CH_2Cl_2/MeOH 9:1) to give the title compound. MS (LC-MS): 709.1 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 6.04 min.

An alternative method for the N-Boc deprotection reaction is described in the following example:

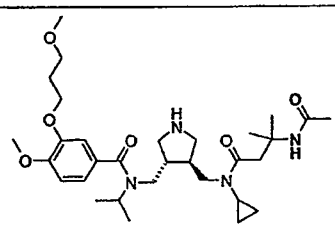
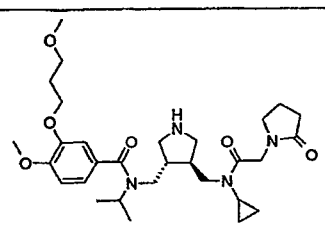
Example 13 : N-((3S,4S)-4-{[(3-Acetylamino-3-methyl-butyryl)-cyclopropyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

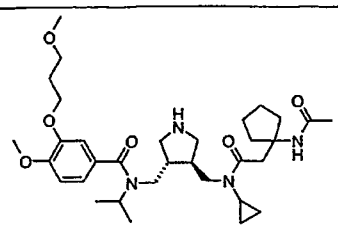
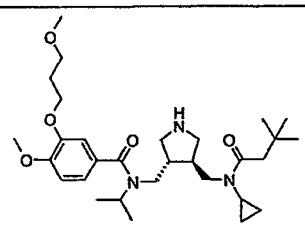
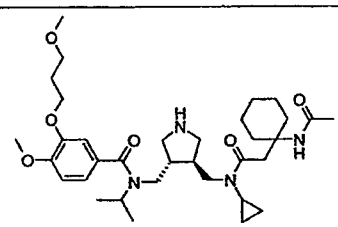
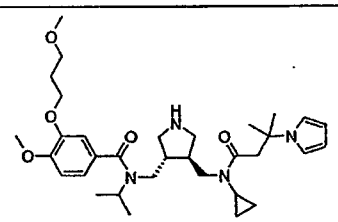
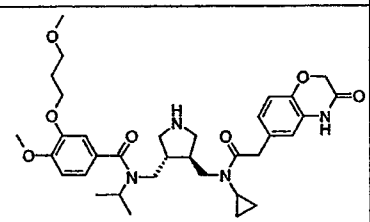
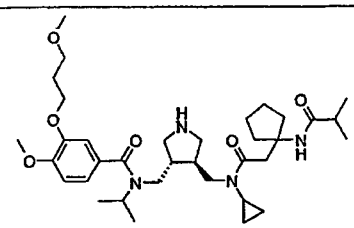


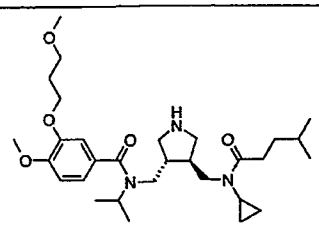
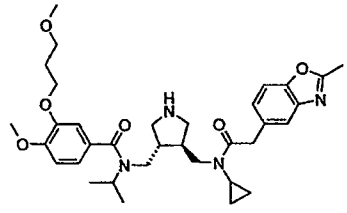
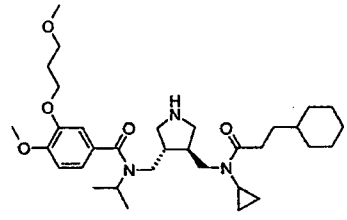
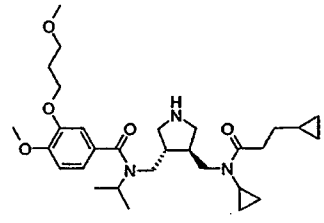
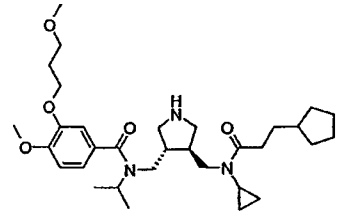
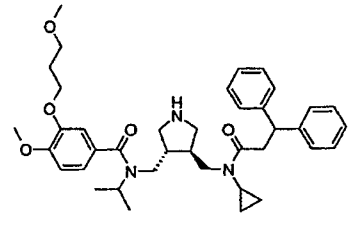
$ZnBr_2$ (110 mg, 0.49 mmol) is added to a solution of (3R,4R)-3-{[(3-acetylamino-3-methyl -butyryl)-cyclopropyl-amino]-methyl}-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (150 mg, 0.22 mmol) in 1,2-dichloroethane (5 mL) and the resulting suspension is stirred at 55°C for 16h. In order to drive the reaction to completion another portion of $ZnBr_2$ (50 mg, 0.22 mmol) is added and heating is continued for another 24 h. For workup a sat. solution of $NaHCO_3$ is added and the mixture is extracted with CH_2Cl_2. Drying (Na_2SO_4) of the combined extracts, filtration and evaporation of the solvent affords the desired product as free base. The free base is dissolved in dioxane (2 mL) and fumaric acid (11 mg, 0.11 mmol) is added. Lyophilization yields the title compound as hemifumarate salt. MS (LC-MS): 575.0 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.90 min.

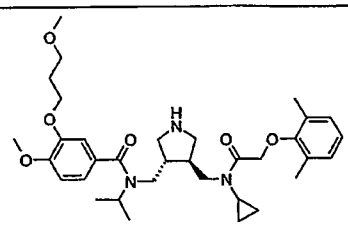
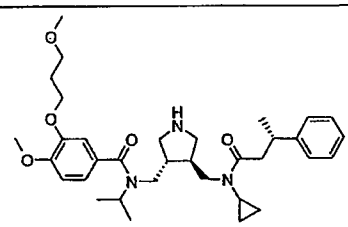
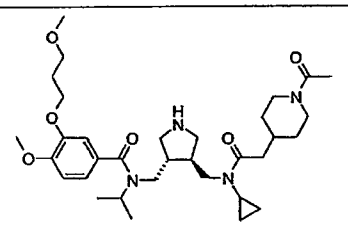
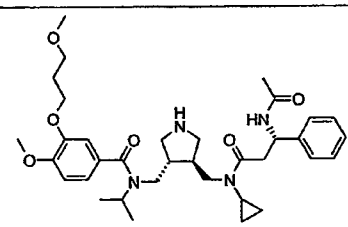
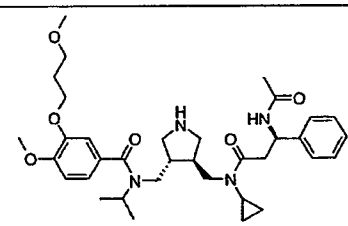
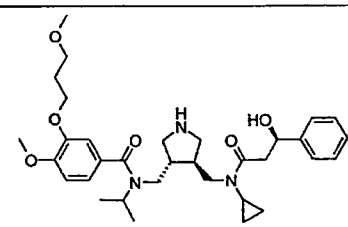
The following Examples are prepared according to the procedures described above in Examples 8, 9, 10, 11, 12 and 13:

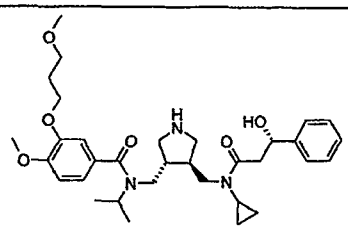
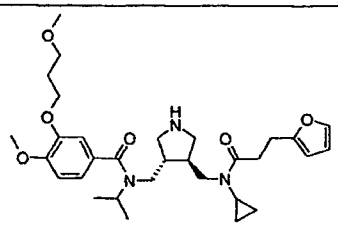
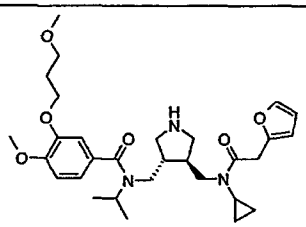
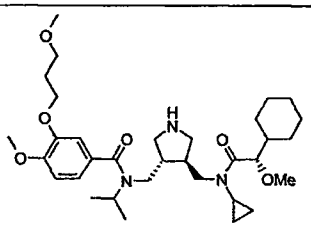
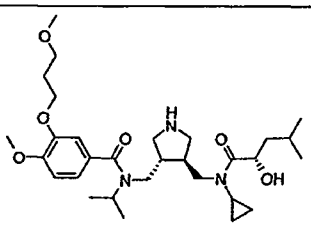
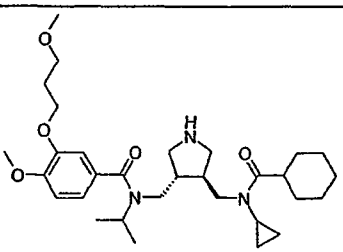
Table 1

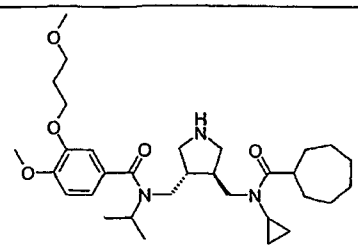
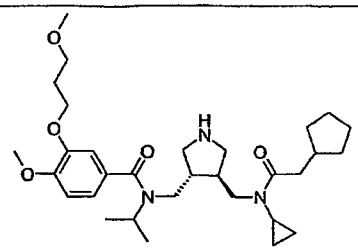
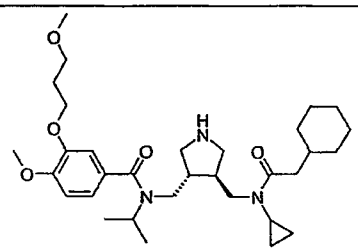
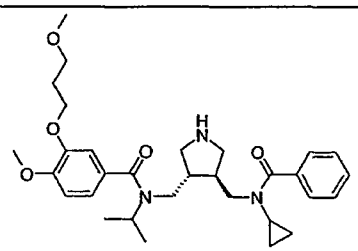
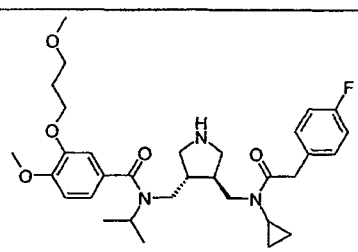
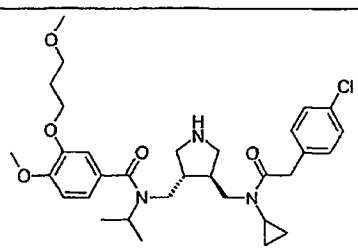
Example	configuration	structure	$[M+H]^+$	t_R (HPLC)
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15	(3S*, 4S*)		559.1	4.04[a]

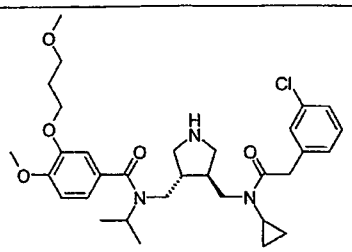
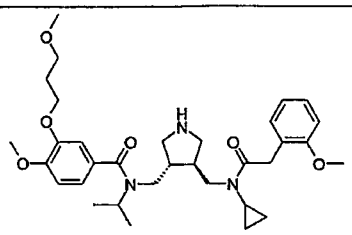
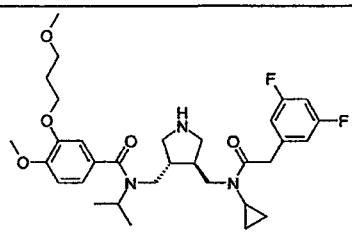
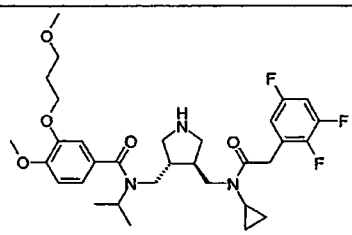
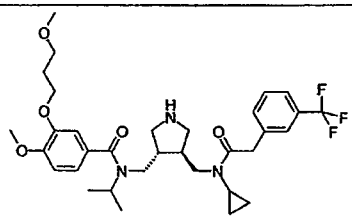
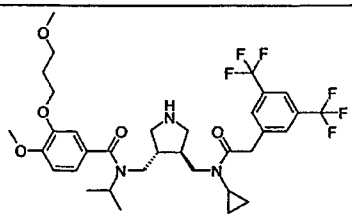
16	(3S*, 4S*)		601.2	4.34[a]
17	(3S*, 4S*)		532.1	4.72[a]
18	(3S*, 4S*)		615.2	4.52[a]
19	(3S*, 4S*)		583.3	4.82[a]
20	(3S*, 4S*)		623.4	4.49[a]
21	(3S*, 4S*)		629.7	4.80[a]

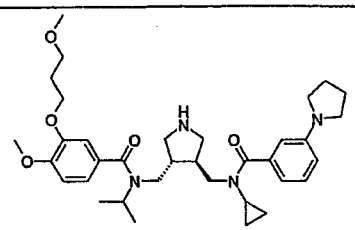
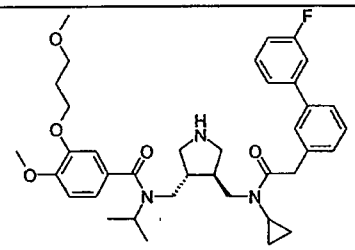
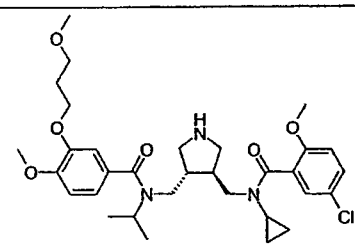
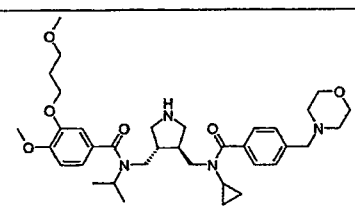
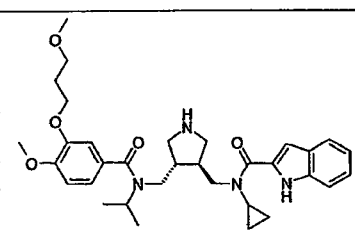
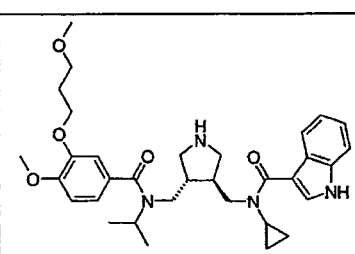
22	(3S*, 4S*)		532.3	5.12[a]
23	(3S*, 4S*)		607.2	5.19[a]
24	(3S*, 4S*)		572.3	5.99[a]
25	(3S, 4S)		530.2	5.87[a]
26	(3S, 4S)		558.3	6.19[a]
27	(3S, 4S)		642.3	5.51[a]

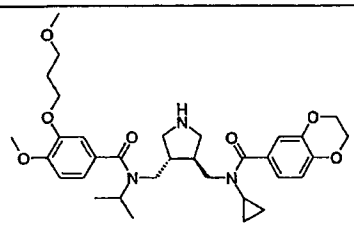
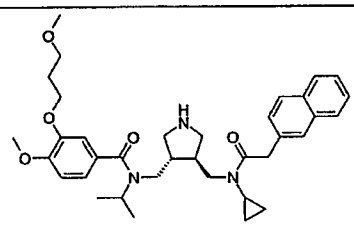
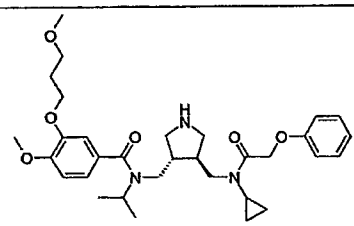
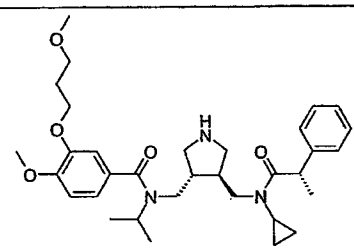
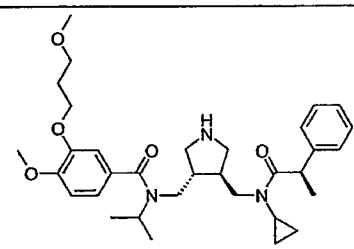
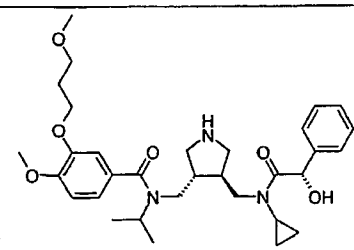
28	(3S, 4S)		596.3	5.44[a]
29	(3S, 4S)		580.0	4.95[a]
30	(3S, 4S)		601.5	3.04[b]
31	(3S, 4S)		623.5	0.36[b]
32	(3S, 4S)		623.5	0.35[b]
33	(3S, 4S)		582.2	4.46[a]

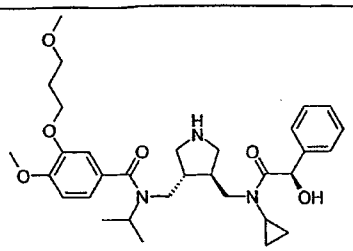
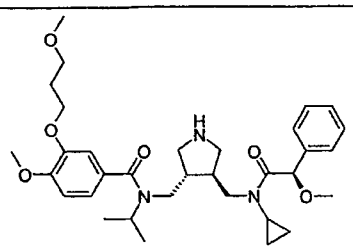
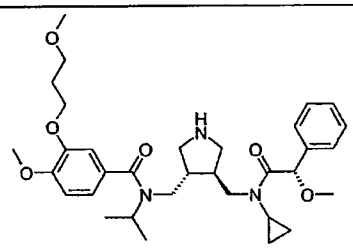
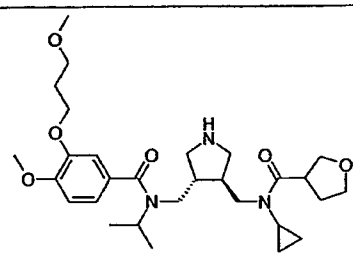
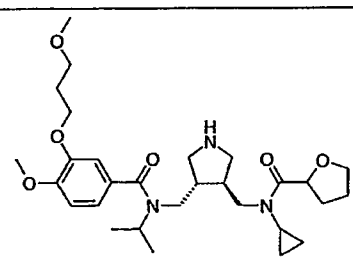
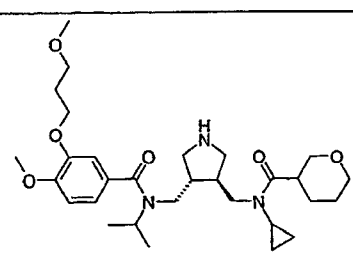
34	(3S, 4S)		582.2	4.50[a]
35	(3S, 4S)		556.3	4.67[a]
36	(3S, 4S)		542.2	4.48[a]
37	(3S, 4S)		588.3	2.89[c]
38	(3S, 4S)		548.2	2.41[d]
39	(3S*, 4S*)		544.4	4.69[e]

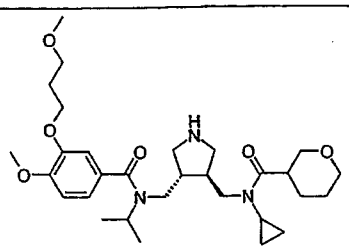
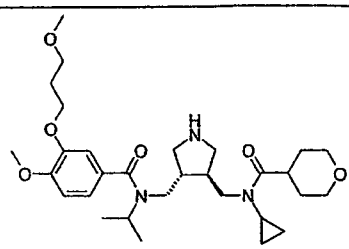
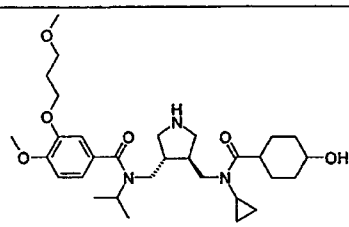
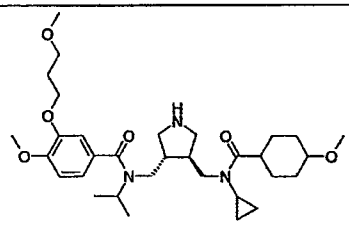
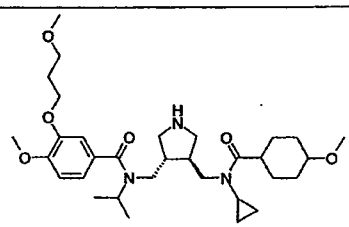
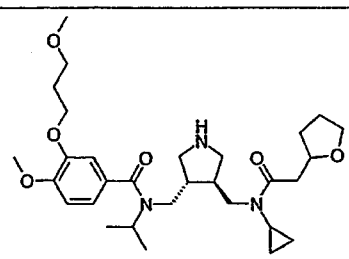
40	(3S,4S)		558.2	4.48[f]
41	(3S,4S)		544.3	4.97[e]
42	(3S*, 4S*)		558.4	5.28[e]
43	(3S*, 4S*)		538.2	4.61[e]
44	(3S*, 4S*)		570.2	4.85[e]
45	(3S,4S)		586.2	5.04[e]

46	(3S*, 4S*)		587.3	4.79[e]
47	(3S*, 4S*)		582.3	4.58[e]
48	(3S*, 4S*)		588.2	4.36[f]
49	(3S*, 4S*)		606.2	4.99[e]
50	(3S*, 4S*)		620.2	4.67[f]
51	(3S*, 4S*)		688.2	5.58[e]

52	(3S*, 4S*)		607.4	3.96[e]
53	(3S*, 4S*)		646.4	5.18[e]
54	(3S*, 4S*)		602.2	4.30[f]
55	(3S*, 4S*)		637.3	2.93[f]
56	(3S*, 4S*)		577.3	4.91[e]
57	(3S*, 4S*)		577.3	4.54[e]

58	(3S,4S)		596.2	3.76[f]
59	(3S*, 4S*)		602.2	5.11[f]
60	(3S,4S)		568.2	4.04[f]
61	(3S*, 4S*)		566.4	4.96[e]
62	(3S*, 4S*)		566.4	4.92[e]
63	(3S,4S)		568.2	3.54[f]

64	(3S,4S)		568.2	3.52[f]
65	(3S,4S)		582.2	3.78[f]
66	(3S,4S)		582.2	3.80[f]
67	(3S*,4S*)		532.2	3.29[f]
68	(3S*,4S*)		532.2	3.32[f]
69	(3S,4S)		546.2	3.40[f]

70	(3S,4S)		546.2	3.41[f]
71	(3S*, 4S*)		546.4	4.21[e]
72	(3S,4S)		560.2	3.10[f]
73	(3S,4S)		574.2	3.82[f]
74	(3S,4S)		574.2	3.60[f]
75	(3S,4S)		546.2	3.46[f]

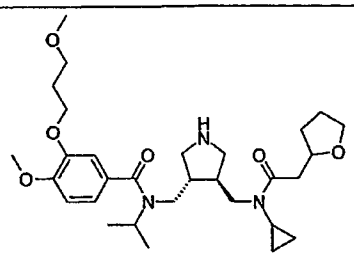
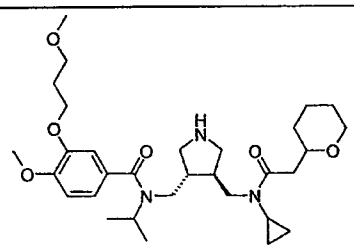
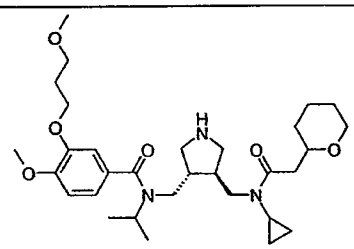
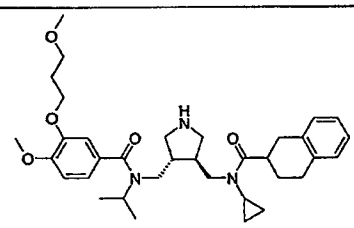
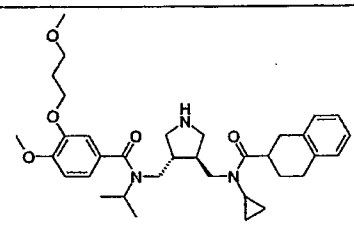
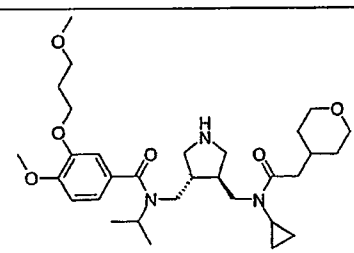
with CH_2Cl_2 and the combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude material is used in the next step without further purification. TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0.39. MS (LC-MS): 387.2 $[M+H]^+$.

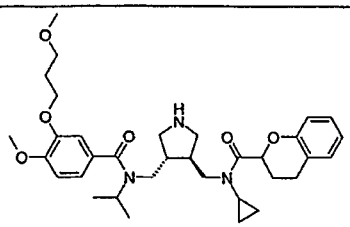
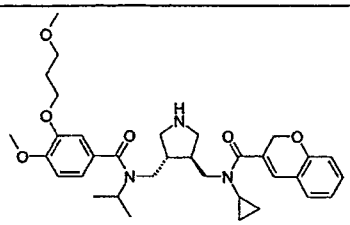
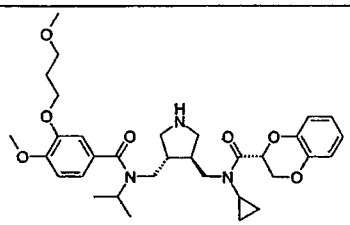
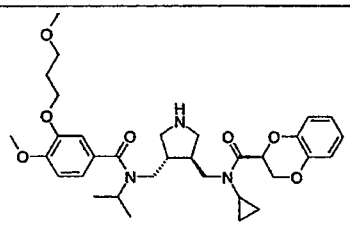
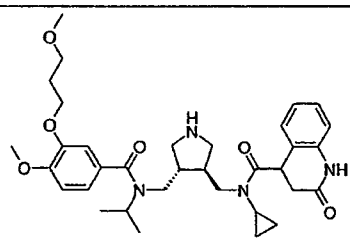
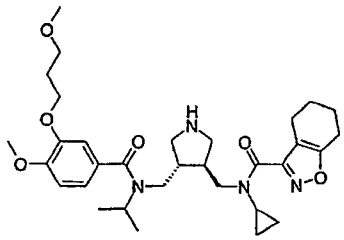
G. (3S,4R)-3-(tert-Butyl-dimethyl-silanyloxymethyl)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

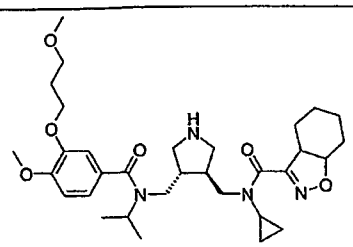
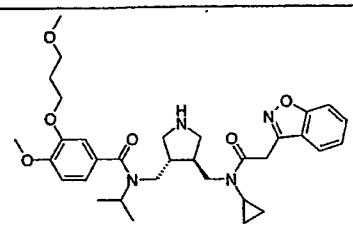
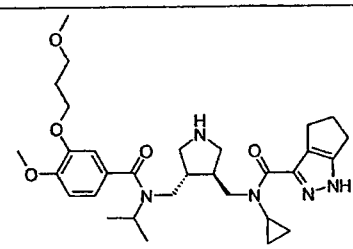
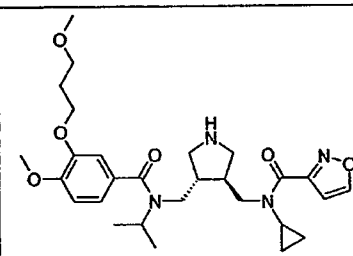
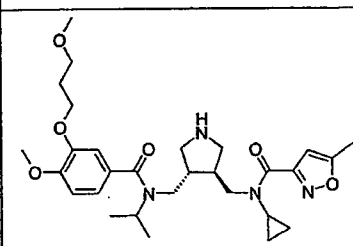
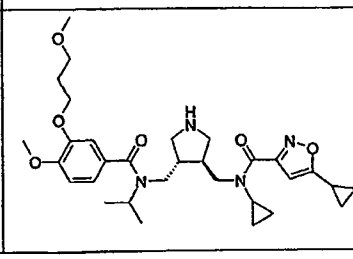
A mixture of ((3S,4R)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-(isopropylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (8.9 g, 23.02 mmol), 3-(3-methoxy-propoxy)-4-methoxy-benzoic acid (6.08 g, 25.32 mmol), bis(2-oxo-3-oxazolidinyl)phosphinic chloride (6.45 g, 25.32 mmol) and triethylamine (7.62 mL, 92.07 mmol) in CH_2Cl_2 (230 mL) is refluxed for 3 h. The reaction is quenched by the addition of an aqueous saturated solution of $NaHCO_3$. The organic layer is separated, and the aqueous phase is extracted 3 times with AcOEt. The combined organic extracts are dried (Na_2SO_4), and the solvent is removed *in vacuo*. The crude product is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/acetone 95:5 to CH_2Cl_2/MeOH 95:5) to give the title product. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.47. MS (LC-MS): 609.4 $[M+H]^+$; t_R (HPLC, C18 column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 7.05 min.

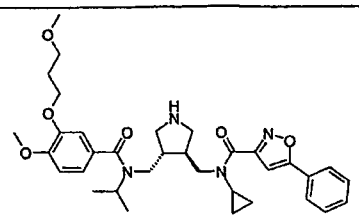
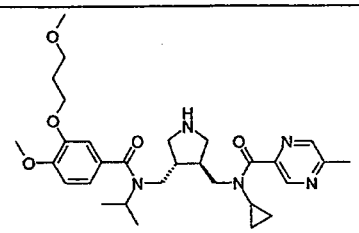
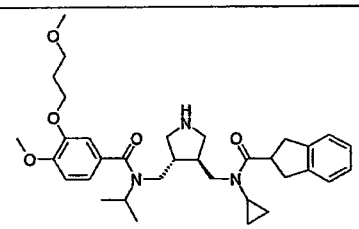
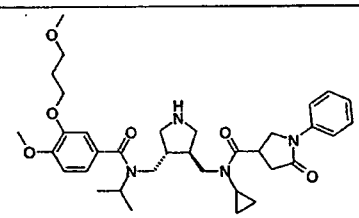
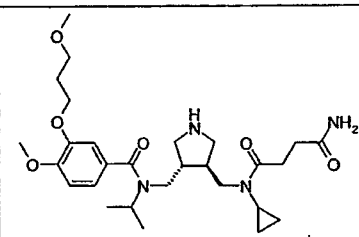
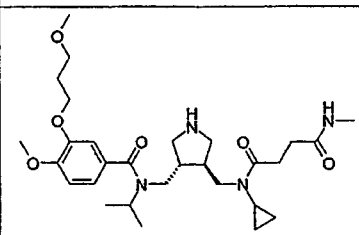
H. (3S,4R)-3-Hydroxymethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

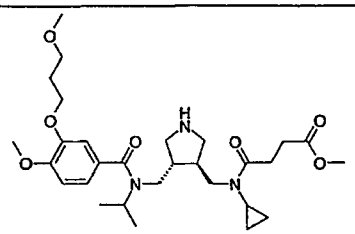
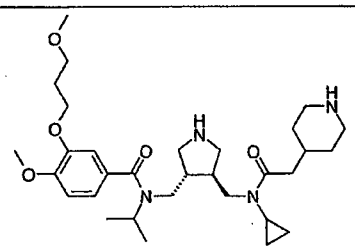
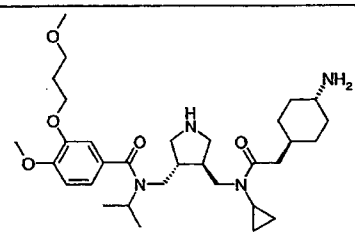
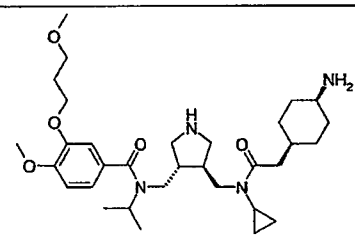
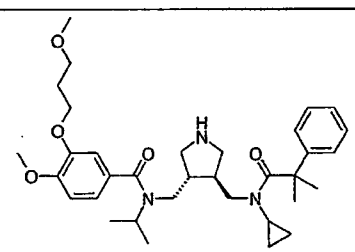
To a solution of (3S,4R)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (8.75 g, 14.37 mmol) in THF (50 mL) is added tetrabutylammonium fluoride trihydrate (6.8 g, 24.55 mmol) under a nitrogen atmosphere. The reaction mixture is stirred overnight. Water and AcOEt are added, the layers are separated and the aqueous one extracted twice with AcOEt. The combined organic extracts are dried (Na_2SO_4), and the solvent is removed *in vacuo*. The crude product is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 97:3 to 95:5) to give the title product. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.3. MS (LC-MS): 395.1 [M+H-Boc]+; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 5.01 min.

76	(3S,4S)		546.2	3.48[f]
77	(3S,4S)		560.2	3.75[f]
78	(3S,4S)		560.2	3.72[f]
79	(3S,4S)		592.2	4.47[f]
80	(3S,4S)		592.2	4.46[f]
81	(3S*, 4S*)		560.4	4.08[e]

82	(3S,4S)		594.2	4.28[f]
83	(3S,4S)		592.2	4.20[f]
84	(3S,4S)		596.2	4.80[e]
85	(3S,4S)		596.2	4.80[e]
86	(3S,4S)		607.2	3.43[f] /3.50[f]
87	(3S,4S)		583.2	4.00[f]

88	(3S,4S)		585.3	4.73[e]
89	(3S,4S)		593.2	4.02[f]
90	(3S*, 4S*)		568.3	4.21[e]
91	(3S*, 4S*)		529.2	3.37[f]
92	(3S*, 4S*)		543.2	4.39[e]
93	(3S*, 4S*)		569.2	3.88[f]

94	(3S,4S)		605.2	4.97[e]
95	(3S*, 4S*)		554.2	4.15[e]
96	(3S,4S)		578.2	4.38[f]
97	(3S*, 4S*)		621.3	4.52[e]
98	(3S*, 4S*)		533.2	2.91[f]
99	(3S*, 4S*)		547.2	3.00[f]

100	(3S*, 4S*)		548.2	3.49[f]
101	(3S,4S)		559.4	3.75[e]
102	(3S,4S)		573.4	3.81[e]
103	(3S,4S)		573.4	3.81[e]
104	(3S,4S)		580.2	4.35[f]

[a] t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min).

[b] t_R (Waters Symmetry C18 column, 10-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min).

[c] t_R (Waters Symmetry C18 column, 5-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min).

[d] t_R (Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min).
[e] t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min).
[f] t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min).

The starting materials are prepared as follows:

For Examples 73 and 74: (3R,4R)-3-{[Cyclopropyl-cis-(4-methoxy-cyclohexanecarbonyl)-amino]-methyl}-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester and (3R,4R)-3-{[cyclopropyl-trans-(4-methoxy-cyclohexanecarbonyl)-amino]-methyl}-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester are separated by chiral HPLC of the diastereoisomeric mixture (0.77 g) on a Chiralpak AD (20 µM; column 50x500 mm) using n-hexane/isopropanol 4:1 as eluent (flow rate: 100 mL/min, UV 210 nm).

For Examples 75 and 76: (3R,4R)-3-{[Cyclopropyl-(2-tetrahydro-furan-2(R)-yl-acetyl)-amino]-methyl}-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester and (3R,4R)-3-{[cyclopropyl-(2-tetrahydro-furan-2(S)-yl-acetyl)-amino]-methyl}-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester are separated by chiral HPLC of the diastereoisomeric mixture (0.34 g) on a Chiralpak AD (20 µM; column 50x500 mm) using n-hexane/EtOH/MeOH 70:25:5 as eluent (flow rate: 100 mL/min, UV 210 nm).

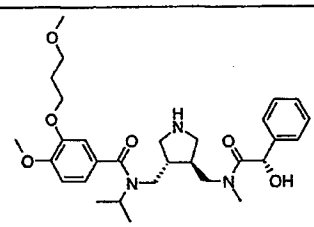
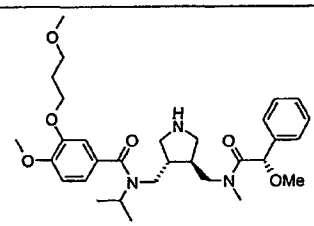
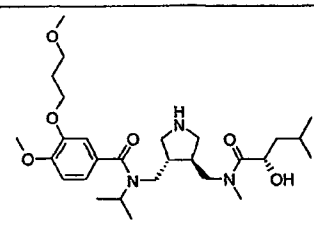
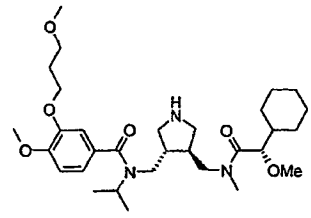
For Examples 77 and 78: (3R,4R)-3-{[Cyclopropyl-(2-tetrahydro-pyran-2(R)-yl-acetyl)-amino]-methyl}-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester and (3R,4R)-3-{[cyclopropyl-(2-tetrahydro-pyran-2(S)-yl-acetyl)-amino]-methyl}-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester are separated by chiral HPLC of the diastereoisomeric mixture (0.32 g) on a Chiralpak AD (20 µM; column 50x500 mm) using a gradient n-hexane/EtOH 90:10 to 85:15 (after 30 min) as eluent (flow rate: 120 mL/min, UV 210 nm).

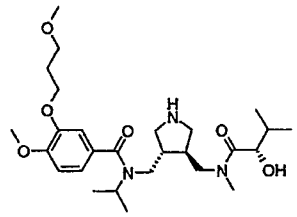
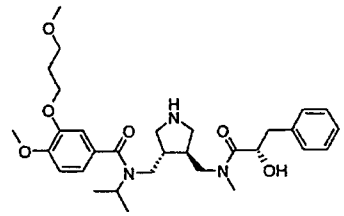
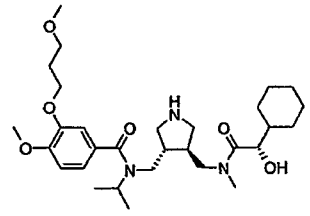
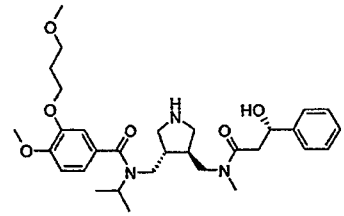
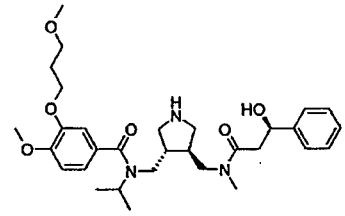
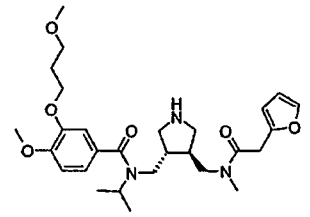
For Examples 79 and 80: (3R,4R)-3-{[Cyclopropyl-(1,2,3,4-tetrahydro-naphthalene-2(R)-carbonyl)-amino]-methyl}-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester and (3R,4R)-3-{[cyclopropyl-(1,2,3,4-

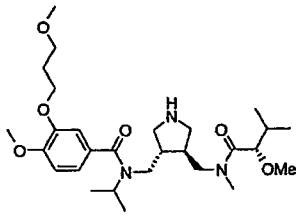
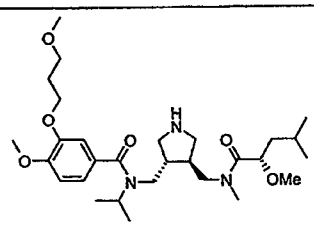
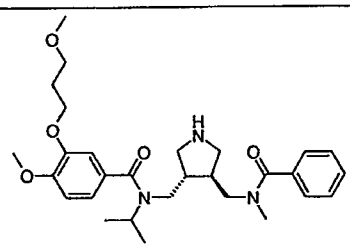
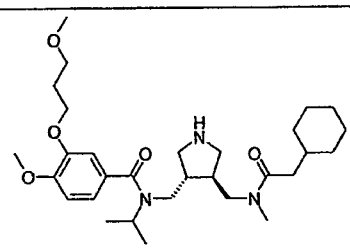
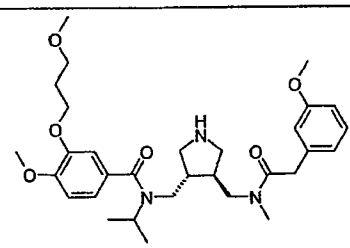
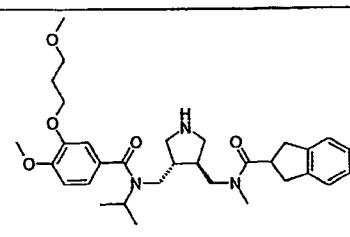
tetrahydro-naphthalene-2(S)-carbonyl)-amino]-methyl}-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester are separated by chiral HPLC of the diastereoisomeric mixture (0.42 g) on a Chiralpak AD (20 µM; column 50x500 mm) using n-hexane/EtOH 4:1 as eluent (flow rate: 50 mL/min, UV 210 nm).

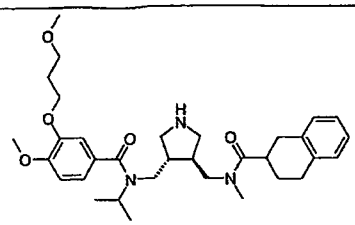
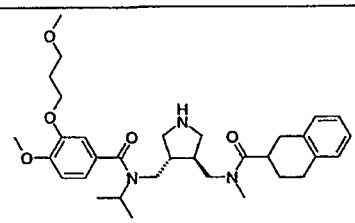
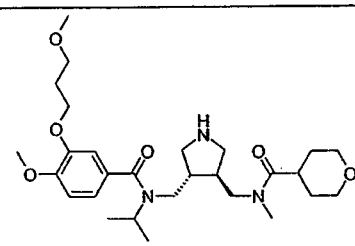
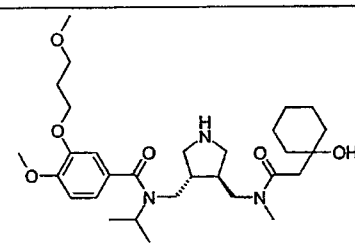
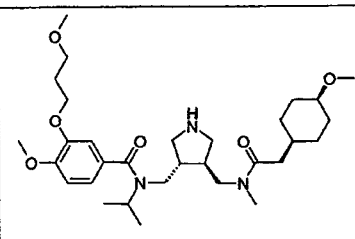
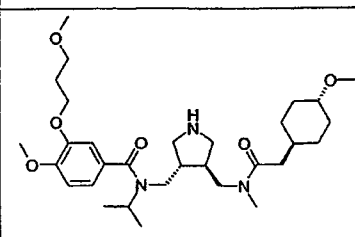
The following Examples are prepared according to the procedures described above in Examples 8, 9, 10, 11, 12 and 13:

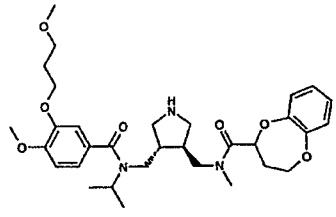
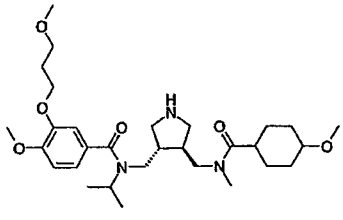
Table 2

Example	configuration	structure	$[M+H]^+$	t_R (HPLC)
105	(3S, 4S)		542.2	4.29[a]
106	(3S, 4S)		556.3	4.43[a]
107	(3S, 4S)		522.2	3.48[d]
108	(3S, 4S)		562.3	2.83[c]

109	(3S, 4S)		508.3	2.59[c]
110	(3S, 4S)		556.3	2.17minb[c]
111	(3S, 4S)		548.3	2.79[c]
112	(3S, 4S)		556.3	1.98[b]
113	(3S, 4S)		556.3	1.77[b]
114	(3S, 4S)		516.3	2.60[c]

115	(3S, 4S)		522.3	1.75[b]
116	(3S, 4S)		536.3	2.39[b]
117	(3S*, 4S*)		512.2	4.09[e]
118	(3S, 4S)		532.4	4.86[e]
119	(3S*, 4S*)		556.3	4.29[e]
120	(3S,4S)		552.2	4.04[f]

121	(3S,4S)		566.2	4.16[f]
122	(3S,4S)		566.2	4.17[f]
123	(3S*, 4S*)		520.3	3.74[e]
124	(3S,4S)		548.2	3.63[f]
125	(3S,4S)		562.3	3.55[f]
126	(3S,4S)		562.2	3.47[f]

127	(3S,4S)		584.3	5.11[f]
128 129	(3S,4S)		548.2	3.25[f] 3.41[f]

[a] t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min).

[b] t_R (Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min).

[c] t_R (Waters Symmetry C18 column, 5-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min).

[d] t_R (Nucleosil C18 HD column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min).

[e] t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min).

[f] t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min).

The starting materials are prepared as follows:

For Examples 121 and 122: (3R,4R)-3-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-{[methyl-(1,2,3,4-tetrahydro-naphthalene-2(R)-carbonyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester and (3R,4R)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-{[methyl-(1,2,3,4-tetrahydro-naphthalene-2(S)-carbonyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester are separated by chiral HPLC of the diastereoisomeric mixture (0.32 g) on a Chiralpak AD (20 µM, column 50x500 mm) using n-hexane/EtOH 1:1 as eluent (flow rate: 50 mL/min, UV 210 nm).

For Examples 128 and 129: (3R,4R)-3-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-{[cis-(4-methoxy-cyclohexanecarbonyl)-methyl-amino]-methyl}-

pyrrolidine-1-carboxylic acid tert-butyl ester and (3R,4R)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-{[trans-(4-methoxy-cyclohexanecarbonyl)-methyl-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester are separated by chiral HPLC of the diastereoisomeric mixture (0.32 g) on a Chiralpak AD (20 µM, column 50x500 mm) using n-hexane/EtOH 1:1 as eluent (flow rate: 50 mL/min, UV 210 nm).

The following intermediates are prepared accordingly:

3-Acetylamino-3-methyl-butyric acid

Triethylamine (1.8 mL, 12.8 mmol), acetic anhydride (1.2 mL, 12.8 mL) and DMAP (10 mg, 0.09 mmol) are subsequentially added to a suspension of 3-amino-3-methyl-butyric acid (1.00 g, 8.5 mmol) in THF (100 mL). After heating at 60°C for 3 h AcOEt is added and the organic phase is washed with 1N HCl. Drying (Na_2SO_4), filtration and evaporation of the solvent yields the desired product. MS (LC-MS): $[M+H]^+$= 160.1. t_R (HPLC, Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min): 0.40 min.

(1-Acetylamino-cyclopentyl)-acetic acid

Triethylamine (1.2 mL, 8.4 mmol), acetic anhydride (0.8 mL, 8.4 mL) and DMAP (10 mg, 0.09 mmol) are subsequentially added to a suspension of (1-amino-cyclopentyl)-acetic acid (1.00 g, 5.6 mmol) in THF (30 mL). After heating at 60°C for 2 h AcOEt is added and the organic phase is washed with 1N HCl. Drying (Na_2SO_4), filtration and evaporation of the solvent yields the desired product. MS (LC-MS): $[M+H]^+$= 186.1. t_R (HPLC, Waters Symmetry C18 column, 80-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min): 0.53 min.

(1-Acetylamino-cyclohexyl)-acetic acid

The title compound is prepared analogously as described for (1-acetylamino-cyclopentyl)-acetic acid from (1-amino-cyclohexyl)-acetic acid. MS (LC-MS): $[M+H]^+$= 200.1. (HPLC, Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min): 0.81 min.

(1-Isobutyrylamino-cyclopentyl)-acetic acid

The title compound is prepared analogously as described for (1-acetylamino-cyclopentyl)-acetic acid from (1-amino-cyclopentyl)-acetic acid. MS (LC-MS): $[M+H]^+$= 214.2. t_R (HPLC,

Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min): 3.08 min.

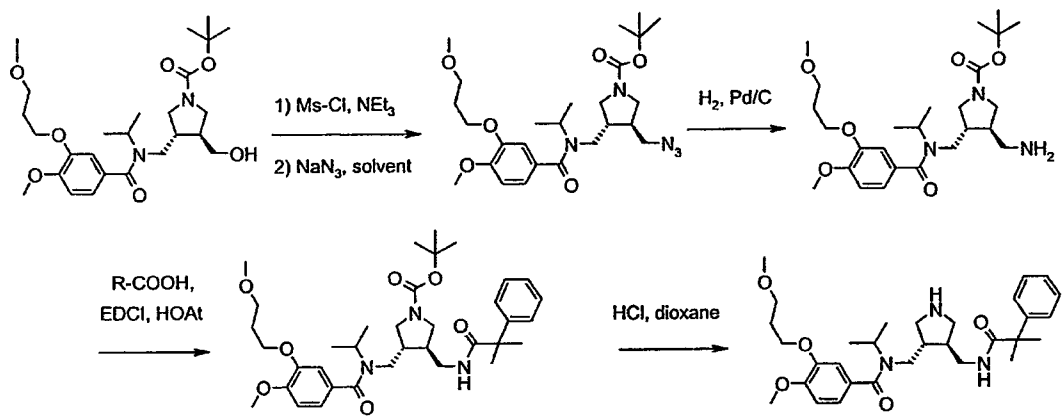
(S)-3-Acetylamino-3-phenyl-propionic acid

The title compound is prepared analogously as described for (1-acetylamino-cyclopentyl)-acetic acid from (S)-3-amino-3-phenylpropionic acid. MS (LC-MS): $[M+H]^+$= 208.2. t_R (HPLC, Waters Symmetry C18 column, 10-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min): 0.79 min.

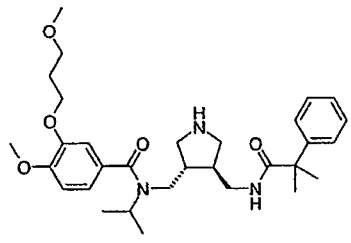
(R)-3-Acetylamino-3-phenyl-propionic acid

The title compound is prepared analogously as described for (1-acetylamino-cyclopentyl)-acetic acid from (R)-3-amino-3-phenylpropionic acid. MS (LC-MS): $[M+H]^+$= 208.2. t_R (HPLC, Waters Symmetry C18 column, 10-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min): 1.16 min.

Scheme 6



Example 130: N-Isopropyl-4-methoxy-3-(3-methoxy-propoxy)-N-{(3S,4S)-4-[(2-methyl-2-phenyl-propionylamino)-methyl]-pyrrolidin-3-ylmethyl}-benzamide



The title compound is prepared according to Scheme 6 as follows: The solution of (3R,4R)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-[(2-methyl-2-phenyl-propionylamino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester (227 mg, 0.319 mmol) in 4N HCl in dioxane (2 mL) is stirred for 6 hrs at room temperature. The volatiles are removed by freeze-drying to give the title compound as white solid. MS $[M+H]^+$ = 540.2. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 3.91 min.

The starting material is prepared as follows:

A. (3R,4S)-3-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-methanesulfonyloxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (3S,4R)-3-hydroxymethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (2.32 g, 4.69 mmol; Example 10, reaction step H) is subsequently added at -20°C with stirring NEt_3 (1.95 mL, 14.1 mmol) and in a dropwise fashion methane sulfonylchloride (0.423 mL, 5.39 mmol). Stirring is continued for 20 min at -20 °C, the mixture is then diluted with CH_2Cl_2 and the organic layer is washed with 2N HCl, dried (Na_2SO_4) and evaporated to dryness to give the crude title compound as yellowish oil. TLC, R_f (hexane/AcOEt 1:3) = 0.13.

B. (3S,4R)-3-Azidomethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (3R,4S)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-methanesulfonyloxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (2.7 g, 4.71 mmol) in DMF (20 mL) is added in one portion NaN_3 (774 mg, 11.8 mmol) and the mixture is stirred at 70 °C overnight. After cooling to room temperature, a saturated aqueous $NaHCO_3$ solution is added, followed by extraction with diethyl ether. The combined organics are washed with brine, dried over Na_2SO_4 and concentrated. The crude product is purified by RP-HPLC on a PrepC_{18} OBD column (dimensions: 30x100 mm; 5 µM particle size, SunFire Ltd) and using a 95-5% gradient of MeCN/H_2O 5:95 (containing 0.1% TFA) to MeCN/H_2O

95:5 (containing 0.1% TFA) over 20 min gives the title compound as colorless oil. TLC, R_f (hexane/AcOEt 1:3) = 0.31. MS: 520.2 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 5.04 min.

C. (3R,4R)-3-Aminomethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

A solution of (3S,4R)-3-azidomethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (1.86 g, 3.58 mmol) in MeOH (40 mL) is hydrogenated overnight in the presence of Pd/C 10% (0.6 g; Engelhard 4505) at room temperature under atmospheric pressure to give, after filtration and drying in vacuo, the title compound as colorless oil. MS: 494.2 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 3.73 min.

D. (3R,4R)-3-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-[(2-methyl-2-phenyl-propionylamino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (3R,4R)-3-aminomethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (200 mg, 0.405 mmol) and α,α-dimethylphenylacetic acid (101 mg, 0.608 mmol) in CH_2Cl_2 (3 mL) is subsequently added Et_3N (0.085 mL, 0.608 mmol), 1-hydroxy-7-azabenzotriazole (84 mg, 0.608 mmol; commercially available from ABCR, AV24631) and N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide HCl (118 mg, 0.608 mmol). Stirring is continued overnight at room temperature, the mixture is then diluted with CH_2Cl_2, and the organic layer is subsequently washed with 2N HCl, saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated. Purification by RP-HPLC on a PrepC_{18} OBD column (dimensions: 30x100 mm; 5 µM particle size, SunFire Ltd) and using a 95-5% gradient of MeCN/H_2O 5:95 (containing 0.1% TFA) to MeCN/H_2O 95:5 (containing 0.1% TFA) over 20 min gives the title compound as colorless oil. MS $[M]^+$ = 640.2. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 5.2 min.

In a similar manner as described in Example 9 for the reaction step J, the following starting materials are prepared, which are used for the preparation of the Examples 137-148 listed in Table 3:

N-((3S*,4R*)-4-Ethylaminomethyl-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide: The title compound is prepared from (3S*,4R*)-3-formyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.75 g, 1.52 mmol), 2N solution of ethylamine in MeOH (3.805 mL, 7.61 mmol) and $NaBH_4$ (0.115 g, 3.04 mmol) and purification by flash chromatography on silica gel (CH_2Cl_2/MeOH 96:4, then CH_2Cl_2/MeOH (10% NH_3 conc.) gradient from 9:1 to 8:2) to give a colorless oil. MS: 522.4 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.47 min.

The corresponding enantiomer **N-((3S,4R)-4-Ethylaminomethyl-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide** is obtained as follows: A solution of (3S,4R)-3-formyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (1.27 g, 2.58 mmol) and gaseous ethylamine (0.704 g, 15.5 mmol; Fluka 02940) in 1,2-dichloroethane (10 mL) is stirred at room temperature for 30 min, then sodium triacetoxyborohydride (1.37 g, 6.45 mmol) is added in one portion and the mixture is stirred overnight. The organic phase is washed with saturated aqueous $NaHCO_3$ solution, the water layers are re-extracted with CH_2Cl_2, and the combined organics are dried (Na_2SO_4) and evaporated to dryness to give the title compound. MS: 522.2 $[M+H]^+$.

N-((3S*,4S*)-4-Cyclobutylaminomethyl-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide: from (3S*,4R*)-3-formyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (1.00 g, 2.03 mmol), cyclobutylamine (0.74 g, 10.2 mmol) and $NaBH_4$ (0.154 g, 4.06 mmol) to give the title compound as oil. TLC, R_f (hexane/AcOEt) = 0.31. MS: 548.3 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.28 min.

N-Isopropyl-N-[(3S*,4S*)-4-(isopropylamino-methyl)-pyrrolidin-3-ylmethyl]-4-methoxy-3-(3-methoxy-propoxy)-benzamide: from (3S*,4R*)-3-formyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.75 g, 1.52 mmol), isopropylamine (0.654 mL, 7.61 mmol) and $NaBH_4$ (0.115 g, 3.04 mmol) and purification by flash chromatography on silica gel (CH_2Cl_2/MeOH 96:4, then CH_2Cl_2/MeOH (10% NH_3 conc.) gradient from 9:1 to 8:2) to give the title compound as colorless oil. MS: 536.4 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.58 min.

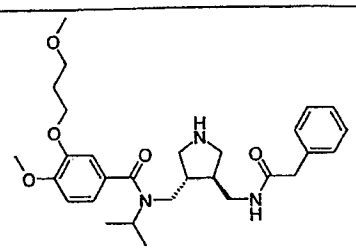
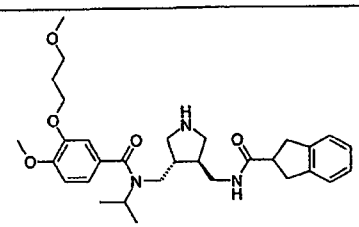
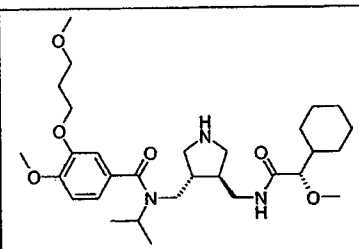
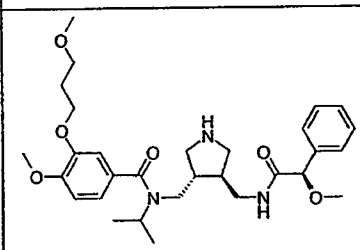
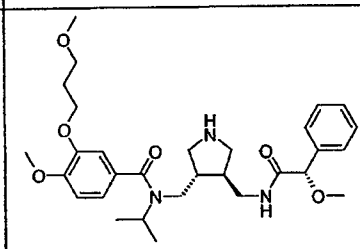
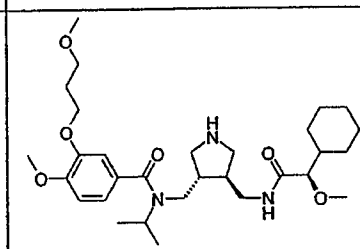
N-[(3S*,4R*)-4-(Isobutylamino-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide: from (3S*,4R*)-3-formyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.75 g, 1.52 mmol), isobutylamine (0.756 mL, 7.61 mmol) and $NaBH_4$ (0.115 g, 3.04 mmol) and purification by flash chromatography on silica gel (CH_2Cl_2/MeOH 96:4, then CH_2Cl_2/MeOH (10% NH_3 conc.) gradient from 9:1 to 8:2) to give the title compound as colorless oil. MS: 550.4 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.74 min.

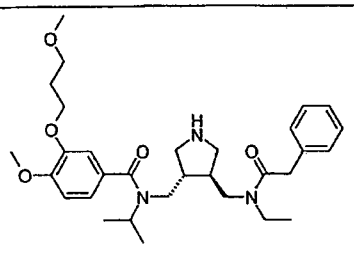
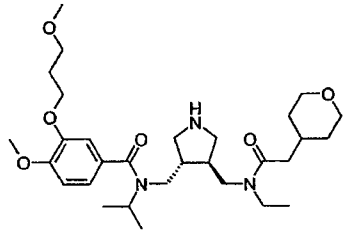
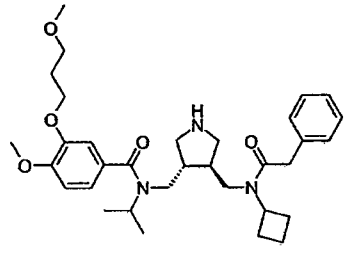
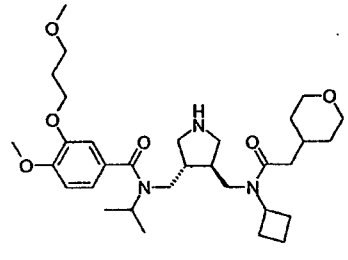
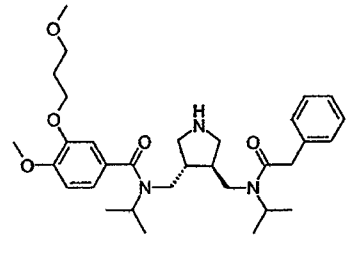
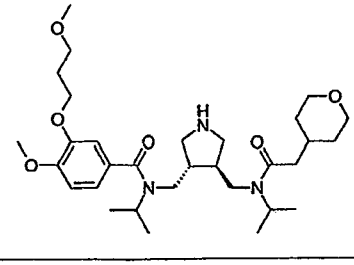
N-{(3S*,4R*)-4-[(Cyclopropylmethyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide: from (3S*,4R*)-3-formyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.75 g, 1.52 mmol), cyclopropanemethylamine (0.652 mL, 7.61 mmol) and $NaBH_4$ (0.115 g, 3.04 mmol) and purification by flash chromatography on silica gel (CH_2Cl_2/MeOH 96:4, then CH_2Cl_2/MeOH (10% NH_3 conc.) gradient from 9:1 to 8:2) to give the title compound as colorless oil. MS: 548.4 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.66 min.

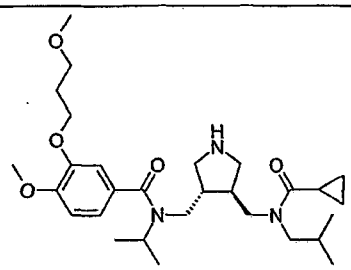
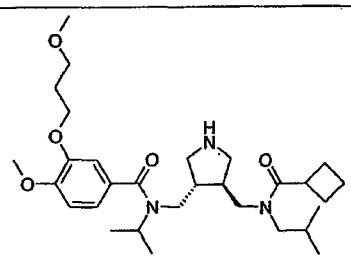
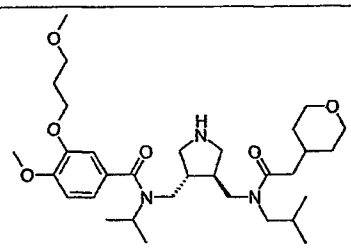
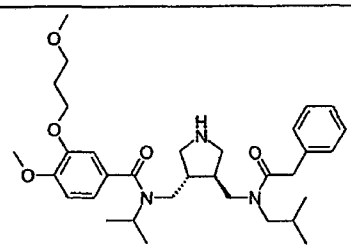
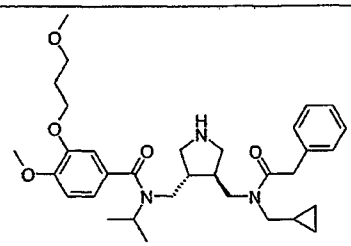
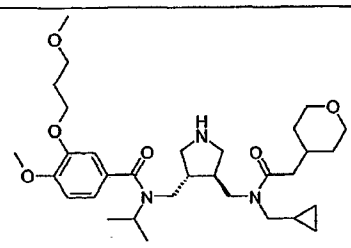
The title compounds in Table 3 are prepared accordingly from the starting materials described above:

Table 3

Example	configuration	structure	$[M+H]^+$	t_R (HPLC)

131	(3S,4S)		512.2	3.47[b]
132	(3S,4S)		538.2	3.83[b]
133	(3S,4S)		548.2	4.00[b]
134	(3S,4S)		542.2	3.59[b]
135	(3S,4S)		542.2	3.57[b]
136	(3S,4S)		548.2	3.98[b]

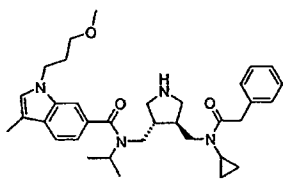
137	(3S,4S)		540.2	3.86[b]
138	(3S,4S)		548.3	4.11[a]
139	(3S*, 4S*)		566.2	4.32[b]
140	(3S*, 4S*)		574.2	3.74[b]
141	(3S*, 4S*)		554.4	4.58[a]
142	(3S*, 4S*)		562.4	4.14[a]

143	(3S*, 4S*)		532.4	4.88[a]
144	(3S*, 4S*)		518.4	4.64[a]
145	(3S*, 4S*)		576.4	4.33[a]
146	(3S*, 4S*)		568.4	4.76[a]
147	(3S*, 4S*)		566.4	4.66[a]
148	(3S*, 4S*)		574.4	4.23[a]

[a] t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min).

[b] t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min).

Example 149: 1-(3-Methoxy-propyl)-3-methyl-1H-indole-6-carboxylic acid {(3S,4S)-4-[(cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-isopropyl-amide



To a solution of (3R,4R)-3-[(cyclopropyl-phenylacetyl-amino)-methyl]-4-({isopropyl-[1-(3-methoxy-propyl)-3-methyl-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.26 g, 0.395 mmol) in dioxane (1 mL), 4N HCl in dioxane (1 mL) is added, and the resulting solution is lyophilized to afford the corresponding hydrochloride salt. MS (LC-MS): 559 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 5.35 min.

The starting material is prepared as follows:

A. (3S,4R)-3-(tert-Butyl-dimethyl-silanyloxymethyl)-4-({isopropyl-[1-(3-methoxy-propyl)-3-methyl-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

A mixture of (3S,4R)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-(isopropylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (8.5 g, 22 mmol), 1-(3-methoxy-propyl)-3-methyl-1H-indole-6-carboxylic acid (7.6 g, 30.8 mmol), bis(2-oxo-3-oxazolidinyl)phosphinic chloride (7.84 g, 30.8 mmol) and triethylamine (12.3 mL, 88 mmol) in CH_2Cl_2 (425 mL) is refluxed overnight under a nitrogen atmosphere and then quenched by the addition of an aqueous saturated solution of $NaHCO_3$. The organic layer is separated, and the aqueous phase is extracted 3 times with AcOEt. The combined organic extracts are concentrated *in vacuo*. The residual oil is taken up in a mixture of THF and MeOH, NaOH 1N is added to cleave the

anhydride side product and the mixture stirred for 3 h. The solvents are concentrated, CH_2Cl_2 is added and the layers are separated. The aqueous one is then back extracted twice with CH_2Cl_2 and the combined organic extracts are washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product is used in the next step without further purification. TLC, R_f (AcOEt) = 0.6. MS (LC-MS): 516.3 $[M\text{-}Boc+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 8.60 min.

B. (3S,4R)-3-Hydroxymethyl-4-({isopropyl-[1-(3-methoxy-propyl)-3-methyl-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (3S,4R)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (13.8 g, 22 mmol) in MeCN (350 mL) is added tetraethylammonium fluoride hydrate (6.6 g, 44 mmol) under a nitrogen atmosphere. The reaction mixture is refluxed for 3 h. Water and AcOEt are added, the layers are separated and the aqueous one extracted twice with AcOEt. The combined organic extracts are dried (Na_2SO_4), filtered and the solvent is removed *in vacuo*. The crude product is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 100:0 to 90:10) to give the title product. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.2. MS (LC-MS): 402.2 [M+H-Boc]+; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 6.85 min.

C. (3S,4R)-3-Formyl-4-({isopropyl-[1-(3-methoxy-propyl)-3-methyl-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound is prepared analogously as described for the title compound under I in Scheme 5 from (3S,4R)-3-hydroxymethyl-4-({isopropyl-[1-(3-methoxy-propyl)-3-methyl-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.6. t_R (HPLC, C18 column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 5.11 min.

D. (3R,4R)-3-Cyclopropylaminomethyl-4-({isopropyl-[1-(3-methoxy-propyl)-3-methyl-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

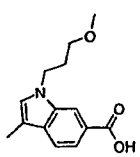
To a solution of (3S,4R)-3-formyl-4-({isopropyl-[1-(3-methoxy-propyl)-3-methyl-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (6 g, 10.9 mmol) in

dichloroethane (100 mL), cyclopropylamine (0.85 mL, 12 mmol) and $NaBH(OAc)_3$ (4.32 g, 15.3 mmol) are added. The solution is stirred at RT overnight, then diluted with CH_2Cl_2. A saturated solution of $NaHCO_3$ is added, the layers are separated and the aqueous one extracted twice with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material is purified by flash chromatography on silica gel (eluent: AcOEt/MeOH 100:0 to 85:15) to give the title compound. TLC, R_f (AcOEt) = 0.1. MS (LC-MS): 541.3 [M+H]+; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.52 min.

E. (3R,4R)-3-[(Cyclopropyl-phenylacetyl-amino)-methyl]-4-({isopropyl-[1-(3-methoxy-propyl)-3-methyl-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound is prepared analogously as described for the title compound under K in Example 9 (Scheme 5) from (3R,4R)-3-cyclopropylaminomethyl-4-({isopropyl-[1-(3-methoxy-propyl)-3-methyl-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester. MS (LC-MS): 658.9 $[M\text{-}Boc+H]^+$. t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 6.69 min.

1-(3-Methoxy-propyl)-3-methyl-1H-indole-6-carboxylic acid



3-Methyl-1H-indole-6-carboxylic acid methyl ester

A mixture of 3-formyl-1H-indole-6-carboxylic acid methyl ester (5 g, 24.6 mmol), p-toluene-sulfonic acid (704 mg, 3.7 mmol) and p-toluenesulfonylhydrazide (5.49 g, 29.5 mmol) in a mixture of dimethylformamide (50 mL) and sulfolane (25 mL) is heated at 100°C for 15 min. Then cooled to RT, before the addition of sodium cyanoborohydride (6.2 g, 98.4 mmol, 2 g portions after 10 min intervals). The resulting mixture is heated at 100°C for 2 h, cooled to RT and poured into a mixture of ice and water (250 mL) leading to a white precipitate. Water (500 mL) is added, and the mixture is stirred for 30 min before filtration. The off-white solid is washed with warm water. Toluene is added and removed by rotary evaporation to afford the

title compound as a yellow solid. TLC, R_f (hexane/AcOEt 4:1)= 0.3. MS (LC-MS): [M+H]+= 188.1. t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 5.13 min.

1-(3-Methoxy-propyl)-3-methyl-1H-indole-6-carboxylic acid methyl ester

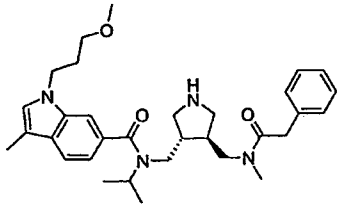
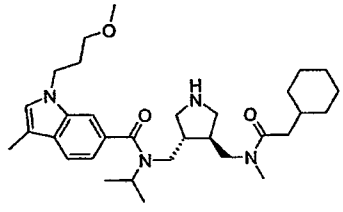
To a solution of 3-methyl-1H-indole-6-carboxylic acid methyl ester (2.5 g, 13.2 mmol) in DMF (25 mL), a solution of NaH (580 mg, 14.5 mmol, 60% dispension in grease) in DMF (25 mL) is slowly added under a N_2 atmosphere. The mixture is stirred at 80°C for 20 min, and cooled to RT before the addition of 1-bromo-3-methoxypropane (4.04 g, 26.4 mmol). The resulting mixture is stirred for 24 h. 1-Bromo-3-methoxypropane (2.02 g, 13.2 mmol) and NaH (580 mg, 14.5 mmol) are added and the mixture further stirred for 24 h to complete the reaction. The solvent is concentrated under reduced pressure and the mixture diluted with AcOEt. An aqueous saturated solution of $NaHCO_3$ is added, the layers are separated, and the aqueous one is back-extracted with AcOEt. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude residue is purified by flash chromatography on silica gel (eluent: c-hexane/AcOEt 80:20) to give the title compound. MS (LC-MS): 262.0 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 5.80 min.

1-(3-Methoxy-propyl)-3-methyl-1H-indole-6-carboxylic acid

To a solution of 1-(3-methoxy-propyl)-3-methyl-1H-indole-6-carboxylic acid methyl ester (1.56 g, 6.3 mmol) in MeOH (20 mL) and H_2O (1 mL) is added NaOH (756 mg, 18.9 mmol) and the mixture is stirred at 50°C overnight. Then neutralized by the addition of water and HCl 1.0 M (3 eq, 18.9 mmol). CH_2Cl_2 is added, the layers are separated, and the aqueous one is extracted twice with CH_2Cl_2. The combined organic layers are dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material is obtained in a pure form and is used in the next step without purification. MS (LC-MS): 248.0 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.93 min.

The following Examples are prepared according to the procedures described above for Example 149 :

Table 4

Example	configuration	structure	$[M+H]^+$	t_R (HPLC)
150	(3S, 4S)		533	5.20[a]
151	(3S, 4S)		539	5.64[a]

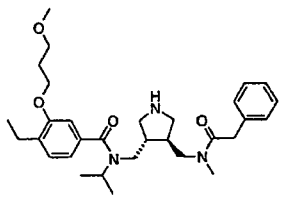
[a] t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min).

The starting materials of the title compounds in Table 4 are prepared as follows:

1-(3-Methoxy-propyl)-3-methyl-1H-indole-6-carboxylic acid {(3S,4S)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-isopropyl-amide

In a similar manner as described in Example 9 for the reaction step J, the following starting material is prepared from (3S,4R)-3-formyl-4-({isopropyl-[1-(3-methoxy-propyl)-3-methyl-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (prepared under C in example 151) (3 g, 5.4 mmol), 2N solution of methylamine in MeOH (13.5 mL, 27 mmol) and $NaBH_4$ (0.408 g, 10.8 mmol) and purification by flash chromatography on silica gel (CH_2Cl_2/MeOH 90:10, then AcOEt/MeOH/NH_4OH 89:10:1) to give a colorless oil. MS: 515.0 $[M+H]^+$.]$^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.41 min.

Example 152 : 4-Ethyl-N-isopropyl-3-(3-methoxy-propoxy)-N-{(3S,4S)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-benzamide



To a solution of (3R,4R)-3-({[4-Ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester (0.330 g, 0.529 mmol) in dioxane (2 mL), 4N HCl in dioxane (2 mL) is added, and the resulting solution is lyophilized to afford the corresponding hydrochloride salt. MS (LC-MS): 524.3 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.94 min.

The starting material is prepared in a similar manner as described in Example 149, reaction steps A to E, as follows:

A. (3S,4R)-3-(tert-Butyl-dimethyl-silanyloxymethyl)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

From (3S,4R)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-(isopropylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (8.5 g, 22 mmol), 4-ethyl-3-(3-methoxy-propoxy)-benzoic acid (5.76 g, 24.2 mmol), BOPCl (6.16 g, 24.2 mmol) and triethylamine (12.3 g, 88 mmol). TLC, Rf (CH_2Cl_2/MeOH 95:5) = 0.32. t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 8.81 min. MS (LC-MS): [M+H-BOC]+ 507.3

B. (3R,4S)-3-({[4-Ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

From (3S,4R)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (13.1 g, 21.6 mmol) and TBAF (17 g, 54 mmol), and purification by flash chromatography on silica gel (CH_2Cl_2/MeOH 95:5) to give the title compound as yellow oil. TLC, Rf (AcOEt) = 0.4,MS (LC-MS): 437.3 $[M+H-tBu]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH3CN/H2O/5 min, 100% CH_3CN/3 min, CH_3CN and H2O containing 0.1% TFA, flow: 1.5 mL/min) : 6.74 min.

C. (3R,4S)-3-({[4-Ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-formyl-pyrrolidine-1-carboxylic acid tert-butyl ester

From (3R,4S)-3-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (8.8 g, 17.9 mmol) and Dess Martin Periodinane (7.6 g, 17.9 mmol) to give the title product as a yellow oil which was used in the next step without purification. TLC, Rf (AcOEt) = 0.55. t_R (tR (HPLC, Waters Symmetry C18, 3.5um, 2.1x50mm, 20-95% CH3CN/H2O/3.5 min, 95% CH3CN/2 min, CH3CN and H2O containing 0.1% HCOOH, flow: 0.6 mL/min): 3.77 min.

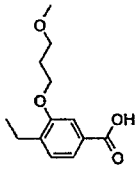
D. (3R,4R)-3-({[4-Ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-methylaminomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

In a similar manner as described in Example 9 for the reaction step J, the following starting materials is prepared from (3R,4S)-3-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-formyl-pyrrolidine-1-carboxylic acid tert-butyl ester (3.5 g, 6 mmol), methyl amine (0.93 mL, 30 mmol) and $NaBH_4$ (0.454 g, 12 mmol) and purification by flash chromatography on silica gel (CH_2Cl_2/MeOH 1:1) to (CH_2Cl_2/MeOH/NH_4OH 89:10:1) to give the title compound as colorless oil. TLC, Rf (CH2Cl2/MeOH/NH4OH 89:10:1) = 0.29. MS (LC-MS): 506.2 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min) : 5.38 min.

E. (3R,4R)-3-({[4-Ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester

From (3R,4R)-3-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-methylaminomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (0.7 g, 1.38 mmol), phenylacetyl chloride (0.22 mL, 1.66 mmol) and triethylamine (0.21 mL, 2.1 mmol) in CH_2Cl_2 (40 mL) and purification by flash chromatography on silica gel (c-hexane/AcOEt 1:1 to 0:1) to give the title compound as colorless oil. TLC, Rf (AcOEt) = 0.30. MS (LC-MS): 624.0 $[M+H]^+$; t_R (Waters Symmetry C18 column, 20-100% CH_3CN/H_2O/5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min) : 4.41 min.

4-Ethyl-3-(3-methoxy-propoxy)-benzoic acid



a. 4-Bromo-3-hydroxy-benzoic acid methyl ester

To a solution of 4-bromo-3-hydroxy-benzoic acid (prepared according to J. Amer. Chem Soc. 1946, 68, 574) (5 g, 32.8 mmol) in MeOH (100 mL), conc. H_2SO_4 (1 mL) is added. The solution is refluxed for 14 h, then concentrated to about 30 mL and poured into a water. The aqueous layer is extracted with ether (50 mL x 4) and the combined organic extracts are neutralized with a saturated aqueous solution of $NaHCO_3$ (50 mL x 2), washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated to give the title compound as a white powder. TLC, R_f (AcOEt) = 0.9. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 5.8 (bs, 1H), 7.45 (d, 1H), 7.55 (d, 1H), 7.7 (s, 1H) ppm.

b. 4-Bromo-3-(3-methoxy-propoxy)-benzoic acid methyl ester

A solution of 4-bromo-3-hydroxy-benzoic acid methyl ester (12 g, 51.9 mmol), potassium carbonate (10.77 g, 77.9 mmol) and 1-iodo-3-methoxy propane (11.42 g, 57.1 mmol) in acetonitrile (250 mL) is stirred at reflux for 16 h. The solvent is concentrated under reduced pressure, H_2O (100 mL) is added, and the aqueous layer extracted with ether (50 mL x 4). The combined organic extracts are washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the title which was used without further purification in the next step. TLC, R_f (hexane/AcOEt 2:1) = 0.65. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 2.12 (p, 2H), 3.38 (s, 3H), 3.63 (t, 2H), 3.9 (s, 3H), 4.2 (t, 2H), 7.5 (d, 1H), 7.55 (m, 1H), 7.6 (d, 1H) ppm.

c. 3-(3-Methoxy-propoxy)-4-trimethylsilanylethynyl-benzoic acid methyl ester

To a stirred solution of 4-bromo-3-(3-methoxy-propoxy)-benzoic acid methyl ester (5 g, 16.49 mmol) and trimethylsilyl actetylene (2.74 mL, 19.8 mmol) in triethylamine (60 mL), $Cl_2Pd(PPh_3)_2$ (2.31 g, 3.29 mmol) and CuI (0.314 g, 1.65 mmol) are added. The resulting mixture is stirred at RT for 15 h and concentrated under reduced pressure. The crude residue is purified by flash chromatography on silica gel (eluent: hexane/AcOEt 10:1 to 5:1) to give the desired title product as a brown oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 0.25 (s, 9H), 2.12 (p, 2H), 3.38 (s, 3H), 3.65 (t, 2H), 3.9 (s, 3H), 4.18 (t, 2H), 7.45 (d, 1H), 7.52 (s, 1H), 7.58 (d, 1H) ppm.

d. 4-Ethynyl-3-(3-methoxy-propoxy)-benzoic acid

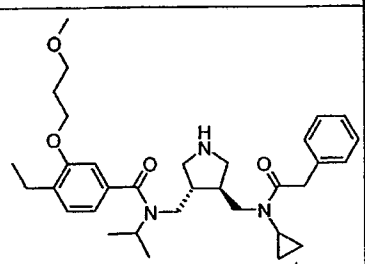
To a solution of 3-(3-methoxy-propoxy)-4-trimethylsilanylethynyl-benzoic acid methyl ester (16.49 mmol) in MeOH (40 mL) is added KOH (1 N, 24.7 mL, 24.7 mmol). The resulting mixture is stirred at RT for 15 h and concentrated under reduced pressure. The residue was taken up in HCl (2 N, 100 mL) and extracted with AcOEt (100 mL x 3). The combined organic extracts are washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the title as a yellow oil which is used without further purification in the next step. MS (FAB): 235.0 $[M+H]^+$.^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 2.15 (p, 2H), 3.38 (s, 3H), 3.41 (s, 1H), 3.62 (t, 2H), 4.22 (t, 2H), 7.5 (d, 1H), 7.65 (s, 1H), 7.68 (d, 1H) ppm.

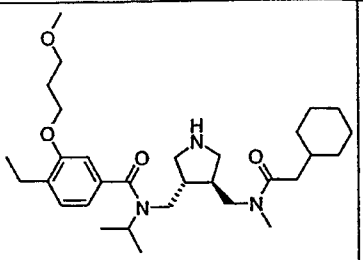
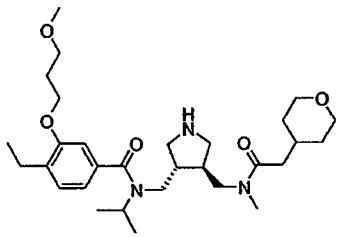
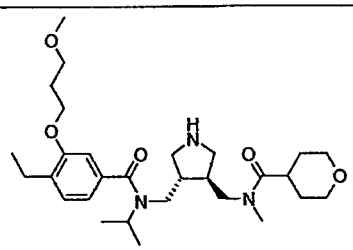
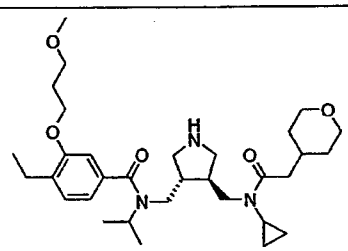
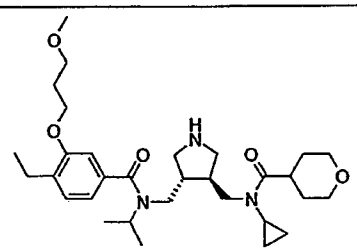
e. 4-Ethyl-3-(3-methoxy-propoxy)-benzoic acid

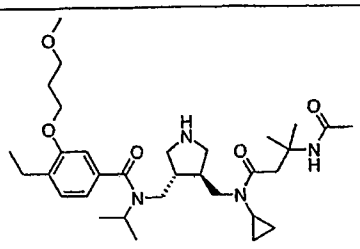
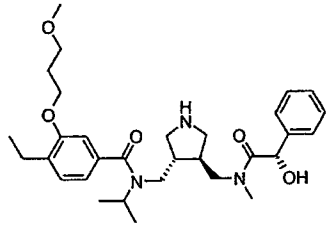
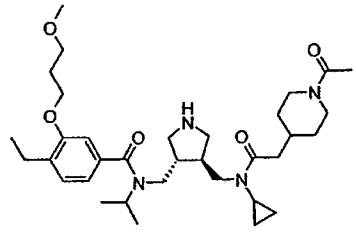
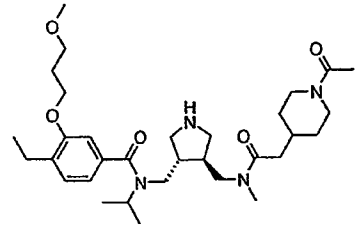
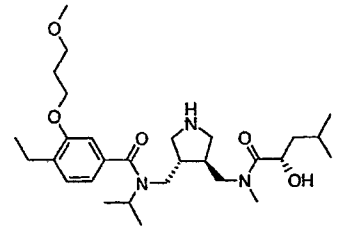
To a solution of 4-ethynyl-3-(3-methoxy-propoxy)-benzoic acid (1 g, 4.11 mmol) in EtOH (20 mL), $Pd(OH)_2$ (0.1 g) is added. The resulting mixture is stirred under an hydrogen atmosphere for 15 min, then filtered and concentrated. The crude material is purified by flash chromatography on silica gel (eluent: hexane/AcOEt 2:1) to give the title compound as white powder. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 1.2 (t, 3H), 2.15 (p, 2H), 2.7 (q, 2H), 3.38 (s, 3H), 3.62 (t, 2H), 4.15 (t, 2H), 7.25 (d, 1H), 7.55 (s, 1H), 7.68 (d, 1H) ppm.

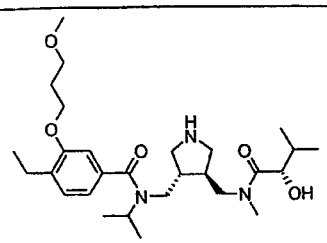
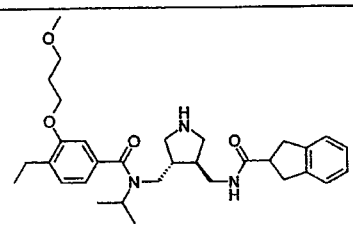
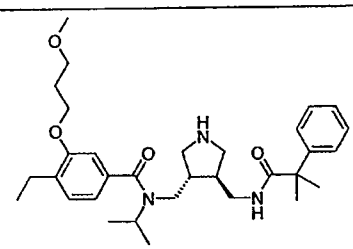
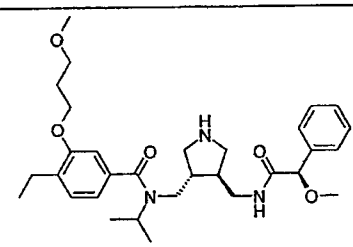
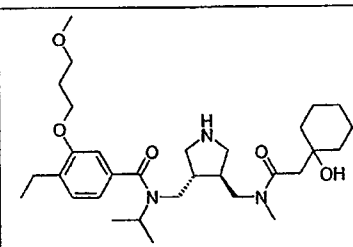
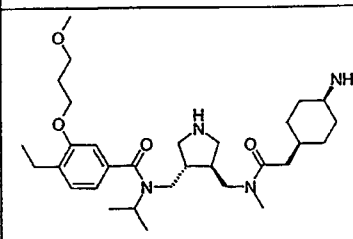
The following Examples are prepared according to the procedures described above for Example 152 :

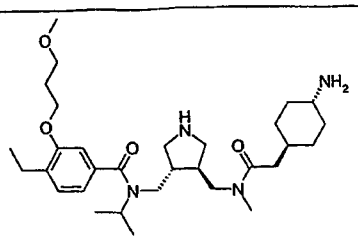
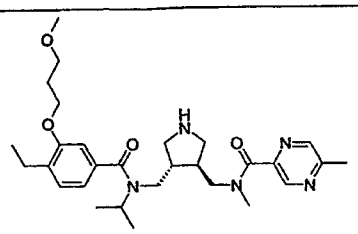
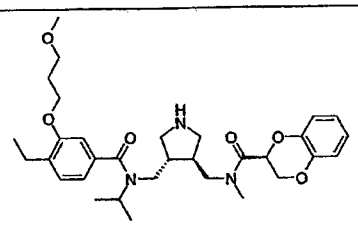
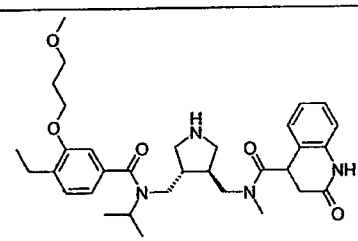
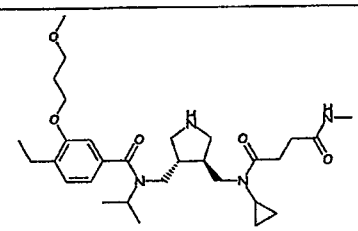
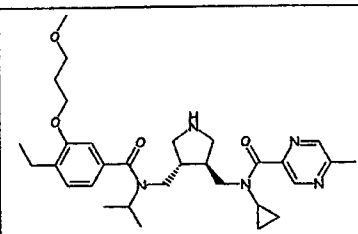
Table 5

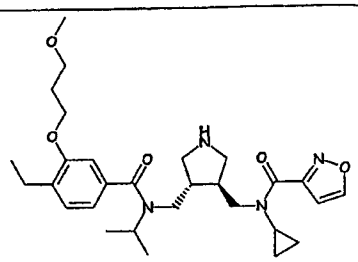
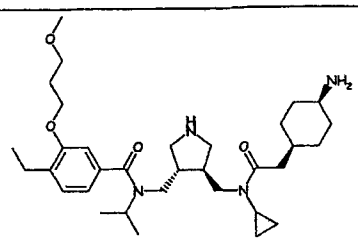
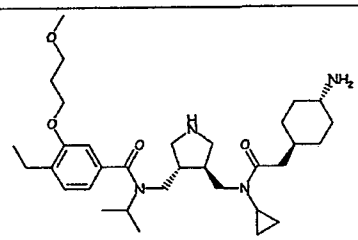
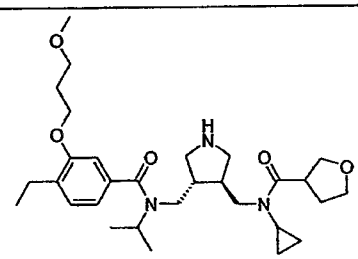
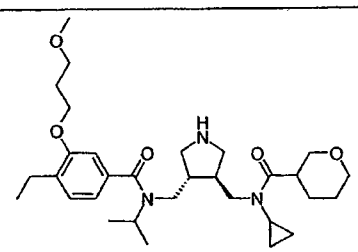
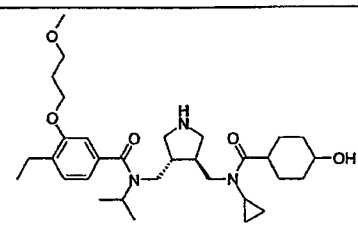
Example	configuration	structure	$[M+H]^+$	t_R (HPLC)
153	(3S, 4S)		550.2	6.13[a]

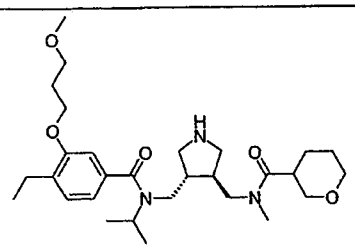
154	(3S, 4S)		530	5.55[a]
155	(3S, 4S)		532	4.10[b]
156	(3S, 4S)		518	3.97[b]
157	(3S, 4S)		558.3	4.37[b]
158	(3S, 4S)		544.3	4.25[b]

159	(3S, 4S)		573.3	2.63[c]
160	(3S, 4S)		540.3	4.88[a]
161	(3S, 4S)		599.2	2.60[c]
162	(3S, 4S)		573.2	2.20[c]
163	(3S, 4S)		520.3	2.94[d]

164	(3S, 4S)		506.4	2.86 min[d]
165	(3S,4S)		536.2	4.71[f]
166	(3S,4S)		538.2	4.76[f]
167	(3S,4S)		540.2	4.47[f]
168	(3S,4S)		546.2	4.52[f]
169	(3S,4S)		545.5	4.26[e]

170	(3S,4S)		545.5	4.25[e]
171	(3S,4S)		526.3	4.69[e]
172	(3S,4S)		568.2	5.24[e]
173 174	(3S,4S)		579.3 579.3	4.78[e] 4.67[e]
175	(3S,4S)		545.3	4.62[e]
176	(3S,4S)		552.3	4.86[e]

177	(3S,4S)		527.2	4.89[e]
178	(3S,4S)		571.4	4.35[e]
1791	(3S,4S)		571.4	4.41[e]
180 181	(3S,4S)		530.2	4.16[f] 4.16[f]
182 183	(3S,4S)		544.2	4.28[f] 4.32[f]
184 185	(3S,4S)		558.3	3.98[f] 4.20[f]

186 187	(3S,4S)		518.2	4.00[f] 4.04[f]

[a] t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min).

[b] t_R (HPLC, Nucleosil C-18HD (4x70mm, 3µm), 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/ 1.5 min; flow: 1 mL/min).

[c] t_R (Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min).

[d] t_R (Waters Symmetry C18 column, 5-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min).

[e] t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min).

[f] t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min).

The starting materials of the title compounds in Table 5 are prepared as follows:

(3R,4R)-3-Aminomethyl-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester:

According to the procedure described for Example 130 / reaction step C, by hydrogenation of (3S,4R)-3-azidomethyl-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (3.95 g, 7.48 mmol), dissolved in absolute EtOH (100 mL), in the presence of Pd/C 10% (0.8 g; Engelhard 4505) at room temperature under atmospheric pressure to give, after filtration and drying in vacuo, the title compound as colorless oil. MS: 492.2 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.62 min.

a. (3R,4S)-3-({[4-Ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-methanesulfonyloxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester: prepared from

(3R,4S)-3-({[4-Ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (4.00 g, 8.12 mmol), methane sulfonylchloride (0.733 mL, 9.34 mmol) and NEt_3 (3.40 mL, 24.4 mmol) in CH_2Cl_2 (50 mL) similar to the procedure described for Example 130 / reaction step A, to give the title compound as yellowish oil. TLC, R_f (hexane/AcOEt 1:3) = 0.32.

b. (3S,4R)-3-Azidomethyl-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester: prepared from (3R,4S)-3-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-methanesulfonyloxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (5.50 g, 8.10 mmol) and NaN_3 (2.13 g, 32.4 mmol) in DMF (40 mL) similar to the procedure described for Example 130 / reaction step B, and purification by flash chromatography on silica gel (hexane/AcOEt 1:1) to give the title compound as colorless oil. TLC, R_f (hexane/AcOEt 1:3) = 0.47. MS: 518.2 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 5.89 min.

(3R,4R)-3-Cyclopropylaminomethyl-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester:

To a solution of (3R,4S)-3-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-formyl-pyrrolidine-1-carboxylic acid tert-butyl ester (described under step C in example 152) (6.9 g, 11.88 mmol) in dichloroethane (112 mL), cyclopropylamine (0.92 mL, 13.1 mmol) and $NaBH(OAc)_3$ (3.52 g, 16.63 mmol) are added. The solution is stirred at RT overnight, then diluted with CH_2Cl_2. A saturated solution of $NaHCO_3$ is added, the layers are separated and the aqueous one extracted twice with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material is purified by flash chromatography on silica gel (eluent: AcOEt/MeOH 100:0 to 85:15) to give the title compound. MS (LC-MS): 532.3 [M+H]+; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.58 min.

The starting materials of Examples 173 and 174 are prepared as follows:

The two diastereomers (3R,4R)-3-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4(R)-{[methyl-(2-oxo-1,2,3,4-tetrahydro-quinoline-4-carbonyl)-amino]-

methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester and (3R,4R)-3-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4(S)-{[methyl-(2-oxo-1,2,3,4-tetrahydro-quinoline-4-carbonyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester are separated by chiral HPLC of the diastereoisomeric mixture (0.5 g) on a Chiralcel OD column (20 mM; 5x50 cm) using n-hexane/EtOH/MeOH 90:7.5:2.5 as eluent (flow 90 mL/min, UV detection 210 nm).

The starting materials of Examples 180 and 181 are prepared as follows:

The two diastereomers (3R,4R)-3-{[cyclopropyl-(tetrahydro-furan-3(R)-carbonyl)-amino]-methyl}-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester and (3R,4R)-3-{[cyclopropyl-(tetrahydro-furan-3(S)-carbonyl)-amino]-methyl}-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester are separated by chiral HPLC of the diastereoisomeric mixture (0.33 g) on a Chiralpak AD column (20 µM; 50x500 mm) using n-hexane/EtOH/MeOH 80:17.5:2.5 (flow rate: 110 mL/min, UV 210 nm).

The starting materials of Examples 182 and 183 are prepared as follows:

The two diastereomers (3R,4R)-3-{[cyclopropyl-(tetrahydro-pyran-3(R)-carbonyl)-amino]-methyl}-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester and (3R,4R)-3-{[cyclopropyl-(tetrahydro-pyran-3-carbonyl)-amino]-methyl}-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester are separated by chiral HPLC of the diastereoisomeric mixture (0.33 g) on a Chiralpak OD column (20 µM; 50x500 mm) using n-hexane/EtOH/MeOH 97:1.5:1.5 (flow rate: 120 mL/min, UV 210 nm).

The starting materials of Examples 184 and 185 are prepared as follows:

The two diastereomers (3R,4R)-3-{[cyclopropyl-cis-(4-hydroxy-cyclohexanecarbonyl)-amino]-methyl}-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-

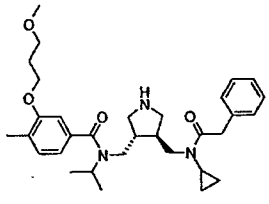
pyrrolidine-1-carboxylic acid tert-butyl ester and (3R,4R)-3-{[cyclopropyl-trans-(4-hydroxy-cyclohexanecarbonyl)-amino]-methyl}-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester are separated by chiral HPLC of

the diastereoisomeric mixture (0.32 g) on a Chiralpak OD column (20 µM; 5x50 cm) using n-hexane/EtOH/MeOH 97:1.5:1.5 as eluent (flow 120 mL/min, UV detection 210 nm).

The starting materials of Examples 186 and 187 are prepared as follows:

The two diastereomers (3R,4R)-3-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-{[methyl-(tetrahydro-pyran-3(R)-carbonyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester and (3R,4R)-3-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-{[methyl-(tetrahydro-pyran-3(S)-carbonyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester are separated by chiral HPLC of the diastereoisomeric mixture (0.28 g) on a Chiralcel AD-H column (30x250 cm) using a gradient 2-propanol/CO_2 (flow 130 mL/min, UV detection 220 nm).

Example 188 : N-{(3S,4S)-4-[(Cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide



To a solution of (3R,4R)-3-[(cyclopropyl-phenylacetyl-amino)-methyl]-4-({[4-methyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.280 g, 0.44 mmol) in dioxane (3 mL), 4N HCl in dioxane (2.5 mL) is added, and the resulting solution is lyophilized to afford the corresponding hydrochloride salt. MS (LC-MS): 536.2 $[M+H]^+$; t_R (HPLC, Nucleosil C-18HD (4x70mm, 3µm), 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/ 1.5 min; flow: 1 mL/min): 4.56 min.

The starting material is prepared in a similar manner as described in Example 149, reaction steps A to E, as follows:

A. (3S,4R)-3-(tert-Butyl-dimethyl-silanyloxymethyl)-4-({[4-methyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

From (3S,4R)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-(isopropylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (5 g, 12.9 mmol), 4-methyl-3-(3-methoxy-propoxy)-benzoic acid (4.06 g, 18.1 mmol), BOPCl (4.6 g, 18.1 mmol) and triethylamine (7.2 mL, 51.7 mmol). TLC, Rf (AcOEt) = 0.7. MS (LC-MS): 493 $[M+H\text{-}Boc]^+$.

B. (3R,4S)-3-({[4-Methyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

From (3S,4R)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-({[4-methyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (6.79 g, 11.5 mmol) and TBAF (5.42 g, 17.2 mmol) to give the title compound as yellow oil which was used in the next step without purification. TLC, Rf (AcOEt) = 0.4. MS (LC-MS): 423 $[M+H\text{-}tBu]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH3CN/H2O/5 min, 100% CH_3CN/3 min, CH_3CN and H2O containing 0.1% TFA, flow: 1.5 mL/min) : 6.05 min.

C. (3R,4S)-3-({[4-Methyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-formyl-pyrrolidine-1-carboxylic acid tert-butyl ester

From (3R,4S)-3-({[4-methyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (5.7 g, 11.9 mmol) and Dess Martin Periodinane (5.1 g, 11.9 mmol) to give the title product as a yellow oil which was used in the next step without purification. TLC, Rf (AcOEt) = 0.49.

D. (3R,4R)-3-({[4-Methyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-cyclopropylaminomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

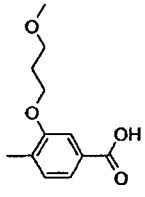
From (3R,4S)-3-({[4-methyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-formyl-pyrrolidine-1-carboxylic acid tert-butyl ester (3 g, 6.29 mmol), cyclopropyl amine (0.395 mL, 6.92 mmol) and $NaBHOAc_3$ (1.87 g, 8.81 mmol) and purification by flash chromatography on silica gel (AcOEt/MeOH 100:0 to 85:15) to give the title compound as colorless oil. TLC, Rf (AcOEt) = 0.63. MS (LC-MS): 518.3 $[M+H]^+$; t_R (HPLC, Nucleosil C-18HD (4x70mm, 3µm), 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/ 1.5 min; flow: 1 mL/min): 5.37 min.

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E. (3R,4R)-3-[(Cyclopropyl-phenylacetyl-amino)-methyl]-4-({[4-methyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

From (3R,4R)-3-({[4-methyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-cyclopropylaminomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (0.3 g, 0.579 mmol), phenylacethyl chloride (0.092 mL, 0.695 mmol) and triethylamine (0.12 mL, 0.869 mmol) and purification by flash chromatography (c-hexane/AcOEt 1:1 to 0:1) to give the title compound as colorless oil. TLC, R_f (AcOEt/c-hexane 4:1) = 0.15. MS (LC-MS): 610.3 $[M+H]^+$; (LC-MS Waters Symmetry C18, 2.1x30mm, 20-100% CH_3CN/5 min) : 4.63 min.

3-(3-Methoxy-propoxy)-4-methyl-benzoic acid



a. 3-Hydroxy-4-methyl-benzoic acid methyl ester

To a solution of 3-hydroxy-4-methyl-benzoic acid (5 g, 32.8 mmol) in MeOH (100 mL) cc H_2SO_4 (1 mL) is added. The solution is refluxed for 14 h, then concentrated to about 30 mL and poured into water. The aqueous layer is extracted with ether (50 mL x 4) and the combined organic extracts are neutralized with a saturated aqueous solution of $NaHCO_3$ (50 mL x 2), washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated to give the title compound as a white powder. TLC, R_f (hexane/AcOEt 2:1) = 0.55. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 2.3 (s, 3H), 3.9 (s, 3H), 7.15 (d, 1H), 7. 5 (d, 1H), 7.6 (s, 1H) ppm.

b. 3-(3-Methoxy-propoxy)-4-methyl-benzoic acid methyl ester

A solution of 3-hydroxy-4-methyl-benzoic acid methyl ester (7.7 g, 32.43 mmol), potassium carbonate (6.72 g, 48.65 mmol) and 1-iodo-3-methoxy propane (7.14 g, 35.68 mmol) in acetonitrile (125 mL) is stirred at reflux for 26 h. The solvent is concentrated under reduced pressure, H_2O (100 mL) is added, and the aqueous layer is extracted with ether (50 mL x 4). The combined organic extracts are washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the title which is used without further purification in the next step. TLC, R_f (hexane/AcOEt 2:1) = 0.65. ^{1}H-NMR ($CDCl_3$, 300 MHz):

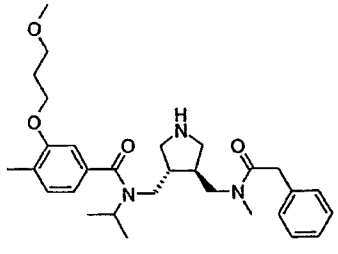
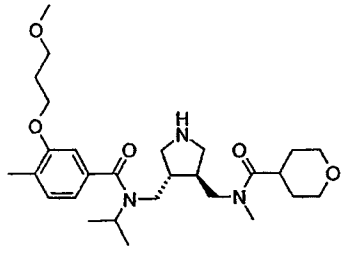
δ = 2.10 (p, 2H), 2.3 (s, 3H), 3.38 (s, 3H), 3.62 (t, 2H), 3.9 (s, 3H), 4.15 (t, 2H), 7.15 (d, 1H), 7.45 (s, 1H), 7.55 (d, 1H) ppm.

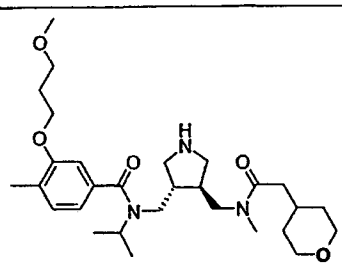
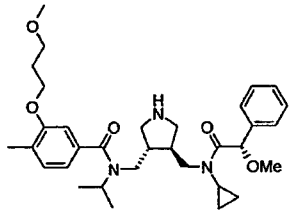
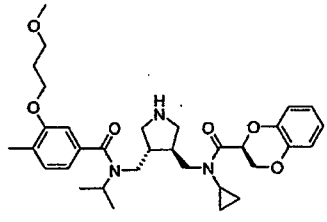
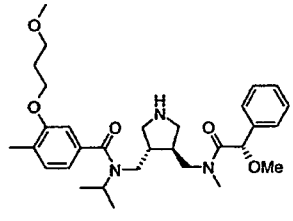
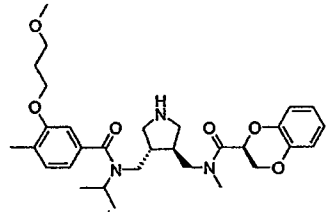
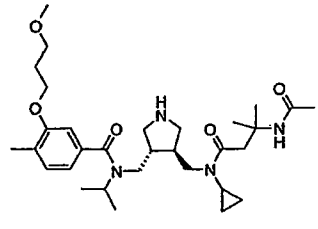
c. 3-(3-Methoxy-propoxy)-4-methyl-benzoic acid

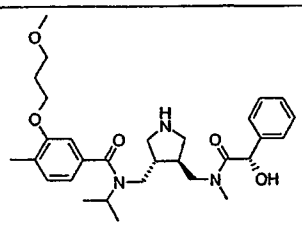
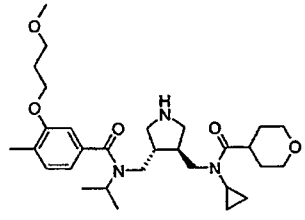
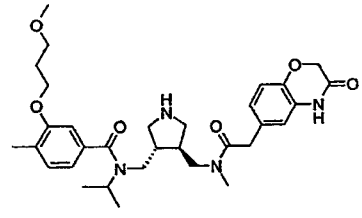
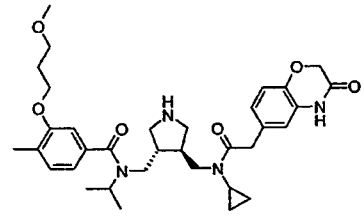
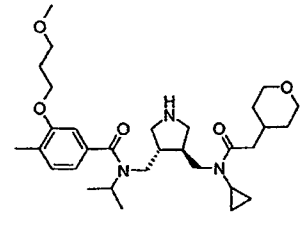
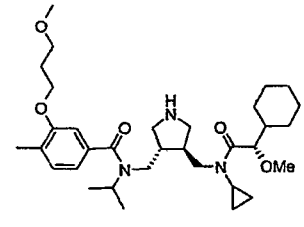
A solution of 3-(3-methoxy-propoxy)-4-methyl-benzoic acid methyl ester (7.12 g, 32.86 mmol) and NaOH (1 N in water, 100 mL, 100 mmol) in EtOH (100 mL) is refluxed for 1 h. The reaction mixture is allowed to reach RT, and the solvent is concentrated under reduced pressure. The residue is dissolved in water (200 mL) and washed with ether (50 mL x 3). The pH is adjusted to 2 by addition of cc HCl and the aqueous layer extracted with AcOEt (150 mL x 2). The combined organic extracts are dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material is recrystallized in diethyl ether/hexane to afford the desired title product. TLC, R_f (hexane/AcOEt 2:1) = 0.15. MS (LC-MS): 224.0 $[M-H]^+$. ^1H-NMR ($CDCl_3$, 300 MHz): δ = 2.10 (p, 2H), 2.3 (s, 3H), 3.38 (s, 3H), 3.62 (t, 2H), 4.15 (t, 2H), 7.2 (d, 1H), 7.55 (s, 1H), 7.65 (d, 1H) ppm.

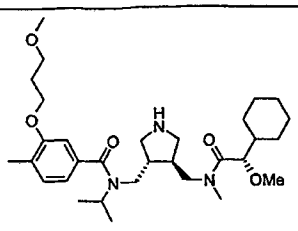
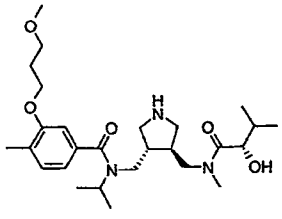
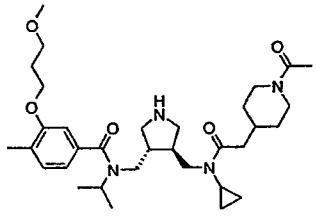
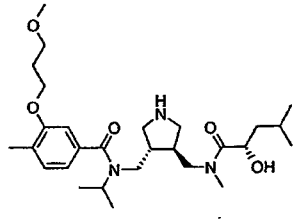
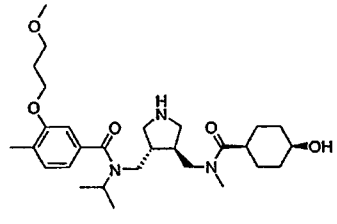
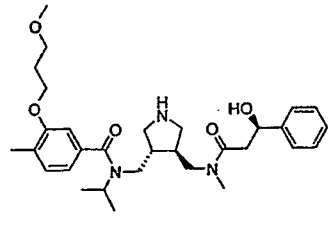
The following Examples are prepared according to the procedures described above for Example 188 :

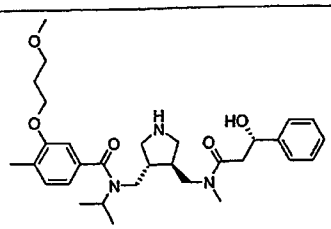
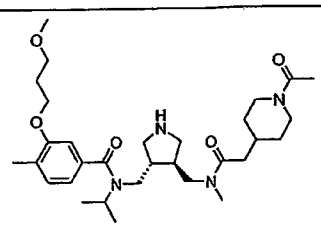
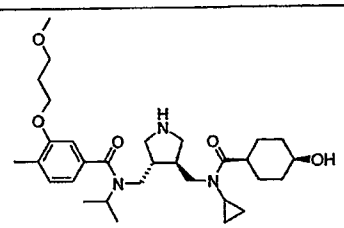
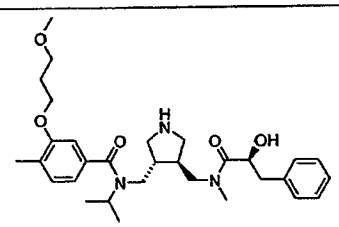
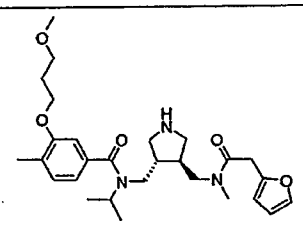
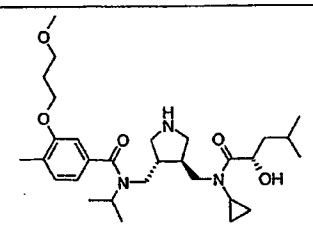
Table 6

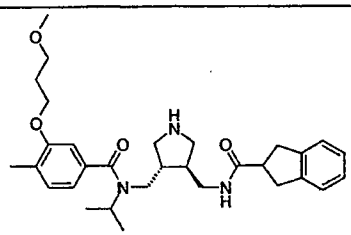
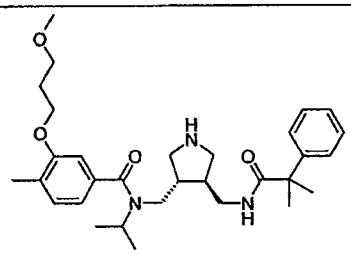
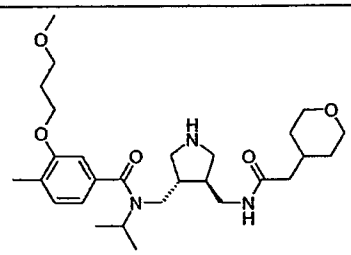
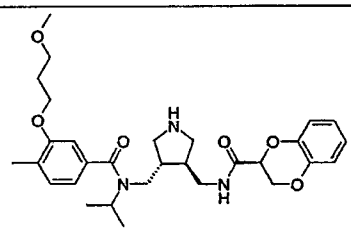
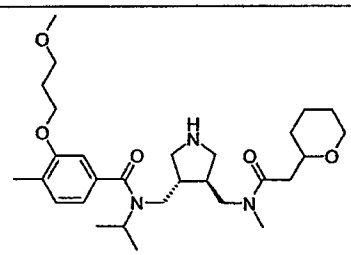
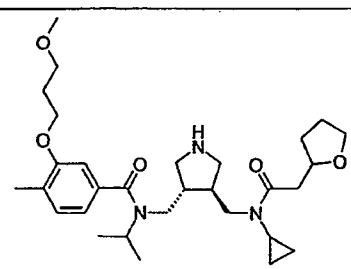
Example	configuration	structure	$[M+H]^+$	t_R (HPLC)
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190	(3S, 4S)		504.4	4.45[a]

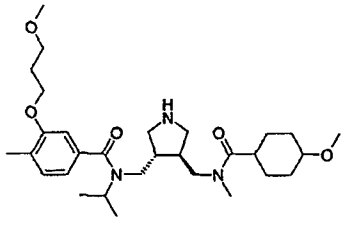
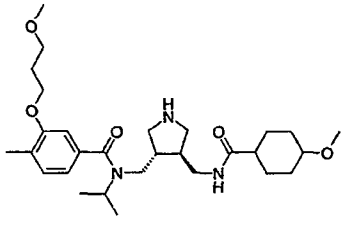
191	(3S, 4S)		518.3	4.47[a]
192	(3S, 4S)		566.2	4.92[a]
193	(3S, 4S)		580.3	5.14[a]
194	(3S, 4S)		540.3	4.81[a]
195	(3S, 4S)		554.2	4.96[a]
196	(3S, 4S)		559.3	4.69[a]

197	(3S, 4S)		526.3	4.71[a]
198	(3S, 4S)		530.3	4.64[a]
199	(3S, 4S)		581.2	2.45[b]
200	(3S, 4S)		607.2	2.60[b]
201	(3S, 4S)		544.2	2.30[b]
202	(3S, 4S)		572.3	3.05[c]

203	(3S, 4S)		546.3	3.02[c]
204	(3S, 4S)		492.3	2.46[b]
205	(3S, 4S)		585.3	2.47[b]
206	(3S, 4S)		506.4	2.82[c]
207	(3S, 4S)		518.3	2.67[c]
208	(3S, 4S)		540.3	2.57[b]

209	(3S, 4S)		540.3	2.61[b]
210	(3S, 4S)		559.2	1.87[b]
211	(3S, 4S)		544.3	2.79[c]
212	(3S, 4S)		540.3	2.66[b]
213	(3S, 4S)		500.2	2.52[b]
214	(3S, 4S)		532.3	2.89[c]

215	(3S,4S)		522.2	4.45[e]
216	(3S,4S)		524.2	4.53[e]
217	(3S,4S)		504.2	3.53[e]
218	(3S,4S)		540.2	4.94[d]
219 220	(3S,4S)		518.3	3.97e 3.99e
221 222	(3S,4S)		530.2	4.07[e] 4.09[e]

223 224	(3S,4S)		532.2	3.92[e] 4.08[e]
225 226	(3S,4S)		518.2	3.76[e] 3.90[e]

[a] t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min).

[b] t_R (Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min).

[c] t_R (Waters Symmetry C18 column, 5-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min).

[d] t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min).

[e] t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min).

The starting materials of the title compounds in Table 6 are prepared as follows:

(3R,4R)-3-Aminomethyl-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester:

According to the procedure described for Example 130/reaction step C, by hydrogenation of (3S,4R)-3-azidomethyl-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (3.68 g, 7.31 mmol), dissolved in MeOH (80 mL), in the presence of Pd/C 10% (1.0 g; Engelhard 4505) at room temperature under atmospheric pressure to give, after filtration and drying in vacuo, the title compound as oil. MS: 478.2 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.28 min.

a. (3R,4S)-3-({Isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-4-methanesulfonyloxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester: prepared from (3S,4R)-3-hydroxymethyl-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (3.80 g, 7.94 mmol), methane sulfonylchloride (0.717 mL, 9.13 mmol) and NEt_3 (3.32 mL, 23.8 mmol) in CH_2Cl_2 (50 mL) similar to the procedure described for Example 130 / reaction step A, to give the title compound as yellowish oil. TLC, R_f (hexane/AcOEt 1:3) = 0.21.

b. (3S,4R)-3-Azidomethyl-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester: prepared from (3R,4S)-3-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-4-methane-sulfonyloxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (4.42 g, 7.94 mmol) and NaN_3 (2.09 g, 31.8 mmol) in DMF (40 mL) similar to the procedure described for Example 130 / reaction step B, and purification by flash chromatography on silica gel (hexane/AcOEt 1:1) to give the title compound as oil. TLC, R_f (hexane/AcOEt 1:3) = 0.45. MS: 504.2 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 5.65 min.

(3R,4R)-3-({[4-Methyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-methylaminomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

In a similar manner as described in Example 9 for the reaction step J, the following starting materials is prepared from (3R,4S)-3-({[4-methyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-formyl-pyrrolidine-1-carboxylic acid tert-butyl ester (prepared under C in example 190) (2 g, 4.2 mmol), 2N solution of methylamine in MeOH (10.5 mL, 21 mmol) and $NaBH_4$ (0.318 g, 8.40 mmol) and purification by flash chromatography on silica gel (AcOEt/MeOH 90:10, then AcOEt/MeOH/NH_4OH 89:10:1) to give a colorless oil. MS: 492.1 $[M+H]^+$.

The starting materials of Examples 219 and 220 are prepared as follows:

The two diastereomers (3R,4R)-3-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-4-{[methyl-(2-tetrahydro-pyran-2(R)-yl-acetyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester and (3R,4R)-3-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-4-{[methyl-(2-tetrahydro-pyran-2(S)-yl-acetyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester are separated by chiral HPLC of the

diastereoisomeric mixture (0.59 g) on a Chiralpak AD column (20 µM; 5x50 cm) using n-hexane/isopropanol 8:2, containing 0.1% TFA, as eluent (flow 100 mL/min, UV detection 210 nm).

The starting materials of Examples 221 and 222 are prepared as follows:

The two diastereomers (3R,4R)-3-{[cyclopropyl-(2-tetrahydro-furan-2(R)-yl-acetyl)-amino]-methyl}-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester and (3R,4R)-3-{[cyclopropyl-(2-tetrahydro-furan-2(S)-yl-acetyl)-amino]-methyl}-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester are separated by chiral HPLC of the diastereoisomeric mixture (0.33 g) on a Chiralpak aD column (20 µM; 5x50 cm) using n-hexane/EtOH/MeOH 80:15:15 as eluent (flow 120 mL/min, UV detection 210 nm).

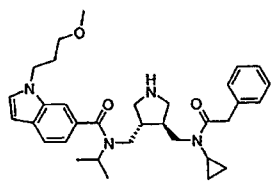
The starting materials of Examples 223 and 224 are prepared as follows:

The two diastereomers (3R,4R)-3-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-4-{[cis-(4-methoxy-cyclohexanecarbonyl)-methyl-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester and (3R,4R)-3-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-4-{[trans-(4-methoxy-cyclohexanecarbonyl)-methyl-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester are separated by chiral HPLC of the diastereoisomeric mixture (0.50 g) on a Chiralpak OD (20 µM; column 5x50 cm) using n-hexane/EtOH/MeOH 97:1.5:1.5 as eluent (flow 120 mL/min, UV detection 210 nm).

The starting materials of Examples 225 and 226 are prepared as follows:

The two diastereomers (3R,4R)-3-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-4-{[cis-(4-methoxy-cyclohexanecarbonyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester and (3R,4R)-3-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-4-{[trans-(4-methoxy-cyclohexanecarbonyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester are separated by chiral HPLC of the diastereoisomeric mixture (0.29 mg) on a Chiralpak OD (20 µM; column 5x50 cm) using n-hexane/EtOH/MeOH 97:1.5:1.5 as eluent (flow 120 mL/min, UV detection 210 nm).

Example 227: 1-(3-Methoxy-propyl)-1H-indole-6-carboxylic acid {(3S,4S)-4-[(cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-isopropyl-amide



To a solution of (3R,4R)-3-[(cyclopropyl-phenylacetyl-amino)-methyl]-4-({isopropyl-[1-(3-methoxy-propyl)-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.15 g, 0.232 mmol) in dioxane (3 mL), 4N HCl in dioxane (1 mL) is added, and the resulting solution is lyophilized to afford the corresponding hydrochloride salt. MS (LC-MS): 545.2 $[M+H]^+$; t_R (HPLC, Waters Symmetry C18, 3.5um, 2.1x50mm, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% HCOOH, flow: 0.6 mL/min): 2.46 min.

The starting material is prepared in a similar manner as described in Example 149, reaction steps A to E, as follows:

A. (3S,4R)-3-(tert-Butyl-dimethyl-silanyloxymethyl)-4-({Isopropyl-[1-(3-methoxy-propyl)-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

From (3S,4R)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-(isopropylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (5 g, 12.9 mmol), 1-(3-methoxy-propyl)-1H-indole-6-carboxylic acid (4.22 g, 18.1 mmol), BOPCl (4.6 g, 18.1 mmol) and triethylamine (7.2 mL, 51.7 mmol). TLC, Rf (AcOEt) = 0.32.

B. (3S,4R)-3-Hydroxymethyl-4-({isopropyl-[1-(3-methoxy-propyl)-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

From (3S,4R)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-({isopropyl-[1-(3-methoxy-propyl)-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (6.79 g, 11.3 mmol) and TBAF (5.35 g, 17.0 mmol) and purification by flash chromatography on silivca gel (chexane/AcOEt 50:50 to 0:100 to AcOEt/MeOH 90:10). TLC, Rf (AcOEt) = 0.34. MS (LC-MS): 432 $[M+H-tBu]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH3CN/H2O/5 min, 100% CH_3CN/3 min, CH_3CN and H2O containing 0.1% TFA, flow: 1.5 mL/min) : 5.73 min.

C. (3S,4R)-3-Formyl-4-({isopropyl-[1-(3-methoxy-propyl)-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester From (3S,4R)-3-

hydroxymethyl-4-({isopropyl-[1-(3-methoxy-propyl)-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (4.3 g, 8.82 mmol) and Dess Martin Periodinane (4.11 g, 9.70 mmol) to give the title product as a yellow oil which was used in the next step without purification.

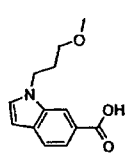
D. (3R,4R)-3-Cyclopropylaminomethyl-4-({isopropyl-[1-(3-methoxy-propyl)-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic

From (3S,4R)-3-formyl-4-({isopropyl-[1-(3-methoxy-propyl)-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (2 g, 4.12 mmol), cyclopropyl amine (0.318 mL, 4.53 mmol) and $NaBHOAc_3$ (1.2 g, 5.77 mmol) and purification by flash chromatography on silica gel (CH_2Cl_2/MeOH 95:5 to CH_2Cl_2/MeOH/NH_4OH 90:10:1). MS (LC-MS): 527.3 $[M+H]^+$; t_R (Waters Symmetry C18, 3.5um, 2.1x50mm, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% HCOOH, flow: 0.6 mL/min): 2.45 min.

E. (3R,4R)-3-[(Cyclopropyl-phenylacetyl-amino)-methyl]-4-({isopropyl-[1-(3-methoxy-propyl)-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

From (3R,4R)-3-cyclopropylaminomethyl-4-({isopropyl-[1-(3-methoxy-propyl)-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic (0.25 g, 0.475 mmol), phenylacethyl chloride (0.069 mL, 0.522 mmol) and triethylamine (0.079 mL, 0.569 mmol) and purification by preparative HPLC (C18-ODB-5 µm, 19x50 mm, eluent: CH_3CN /H_2O + 0.1 % HCOOH). MS (LC-MS): 645.3 $[M+H]^+$; t_R (HPLC, Waters Symmetry C18, 3.5um, 2.1x50mm, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% HCOOH, flow: 0.6 mL/min) : 4.11 min.

1-(3-Methoxy-propyl)-1H-indole-6-carboxylic acid



a. 1-(3-Methoxy-propyl)-1H-indole-6-carboxylic acid methyl ester

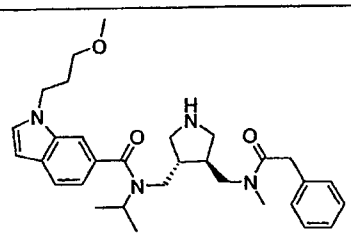
To a solution of methyl indole-6-carboxylate (5.0 g, 28.5 mmol) in DMF (25 mL) is added under nitrogen, NaH-60% dispersion in oil (1.25 g, 31.3 mmol), the mixture is heated at 60°C for 2 h, cooled to RT and 1-bromo-3-methoxypropane (8.7 g, 57.0 mmol) is added. The mixture is further stirred at 60°C overnight. The crude mixture is poured into an aqueous solution of NH_4Cl and diluted with CH_2Cl_2. The layers are separated and the aqueous one extracted twice with CH_2Cl_2. The combined organic extracts are washed with water, dried over Na_2SO_4, filtered and concentrated to give the title product. MS (LC-MS): 248.0 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.69 min.

b. 1-(3-Methoxy-propyl)-1H-indole-6-carboxylic acid

To a solution of 1-(3-methoxy-propyl)-1H-indole-6-carboxylic acid methyl ester (7 g, 28.5 mmol) in MeOH (50 mL) is added NaOH 2N (28.5 mL), and the mixture is stirred for 3 h. The solvent is concentrated and the remaining aqueous residue is acidified with HCl 1N and extracted twice with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated to give title product. TLC, R_f (c-hexane/AcOEt 2:1) = 0.25. MS (LC-MS): 232.0 $[M+H]^+$, t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, flow: 1.5 ml/min): 5.04 min.

The following Example is prepared according to the procedures described above for Example 227:

Table 7

Example	configuration	structure	$[M+H]^+$	t_R (HPLC)
228	(3S, 4S)		519.3	2.32

t_R (HPLC, Waters Symmetry C18, 3.5um, 2.1x50mm, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% HCOOH, flow: 0.6 mL/min).

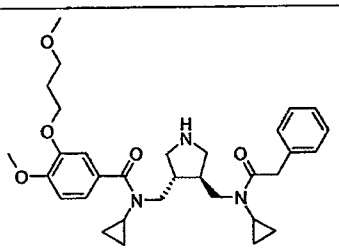
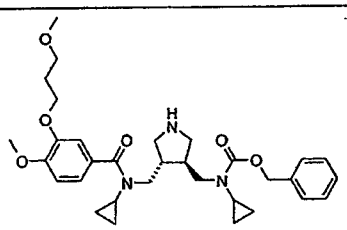
The starting material of the title compound in Table 7 is prepared as follows:

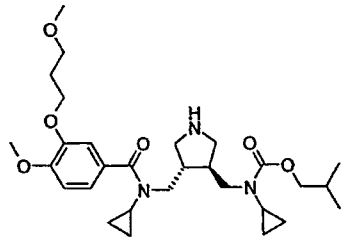
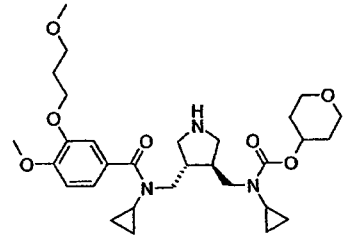
(3R,4R)-3-({Isopropyl-[1-(3-methoxy-propyl)-1H-indole-6-carbonyl]-amino}-methyl)-4-methylaminomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester

In a similar manner as described in Example 9 for the reaction step J, the following starting material is prepared from (3S,4R)-3-formyl-4-({isopropyl-[1-(3-methoxy-propyl)-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (2 g, 4.12 mmol) (prepared under C in example 229), 2N solution of methylamine in MeOH (10.3 mL, 20.6 mmol) and $NaBH_4$ (0.156 g, 4.12 mmol) and purification by flash chromatography on silica gel (CH_2Cl_2/MeOH 95:5 to CH_2Cl_2/MeOH/NH_4OH 90:10:1). MS (LC-MS): 501.3 $[M+H]^+$; t_R (Waters Symmetry C18, 3.5um, 2.1x50mm, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% HCOOH, flow: 0.6 mL/min): 2.40 min.

The following Examples are prepared according to the procedures described above for Examples 227, 233 and 282 using (3R,4R)-3-cyclopropylaminomethyl-4-({cyclopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester:

Table 8

Example	configuration	structure	$[M+H]^+$	t_R (HPLC)
229	(3S, 4S)		550	3.86
230	(3S, 4S)		565.9	5.16

231	(3S, 4S)		532	5.23
232	(3S, 4S)		560.2	3.33

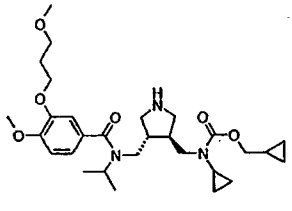
t_R (HPLC, Nucleosil C-18HD, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/1.5 min, flow: 1 ml/min).

The starting material of the title compounds in Table 8 is prepared as follows:

(3R,4R)-3-Cyclopropylaminomethyl-4-({cyclopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

In a similar manner as described in Example 149 for the reaction step D, the following starting material is prepared from (3R,4S)-3-({cyclopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-formyl-pyrrolidine-1-carboxylic acid tert-butyl ester (1.79 g, 3.65 mmol) (prepared according to example 9 using cyclopropyl amine instead of isopropyl amine under F), cyclopropyl amine (0.287 mL, 4.01 mmol) and $NaBHOAc_3$ (1.14 g, 5.11 mmol) to give the title compound which is used in the next steps without further purification. TLC, R_f (CH_2Cl_2/AcOEt 9:1) = 0.35. MS (LC-MS): 532.0 $[M+H]^+$.

Example 233 : Cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid cyclopropylmethyl ester



To a solution of (3S*,4R*)-3-[(cyclopropyl-cyclopropylmethoxycarbonyl-amino)-methyl]-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-

carboxylic acid tert-butyl ester (140 mg, 0.222 mmol) in dioxane (4 mL), 4N HCl in dioxane (2 mL) is added and the resulting solution is stirred at RT for 7h. Lyophilization affords the corresponding hydrochloride salt. MS (LC-MS): 532.1 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.37 min.

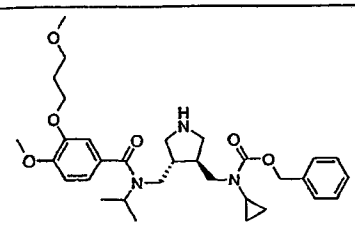
The starting material is prepared as follows:

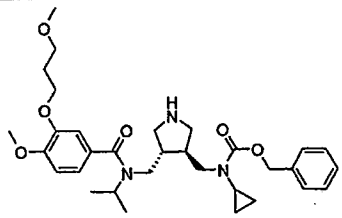
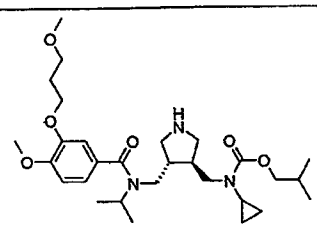
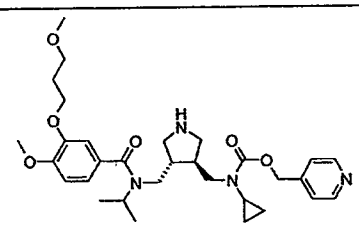
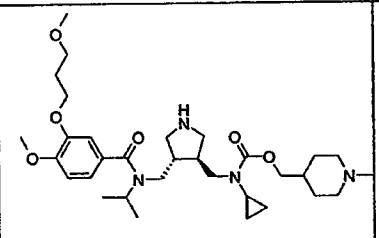
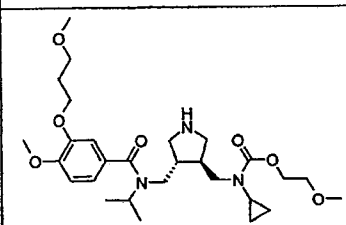
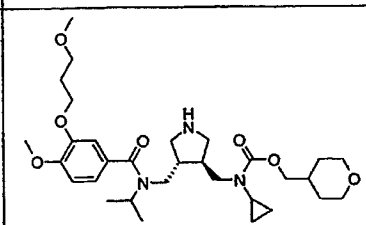
(3S*,4R*)-3-[(Cyclopropyl-cyclopropylmethoxycarbonyl-amino)-methyl]-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

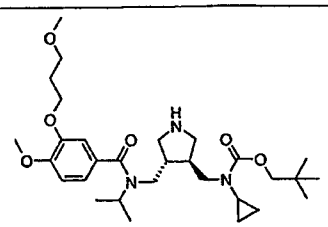
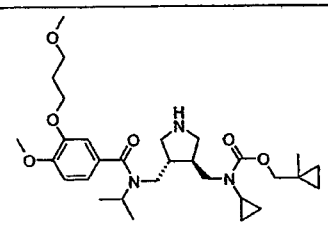
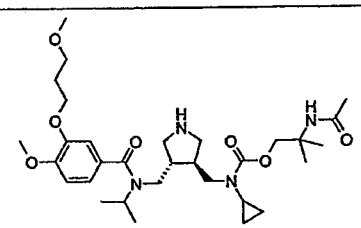
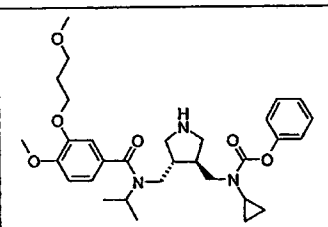
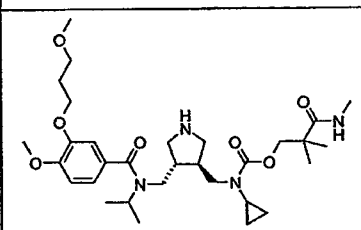
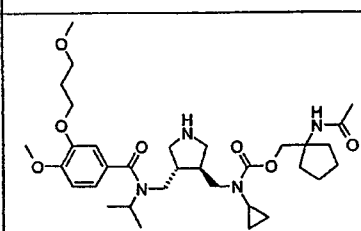
To a solution of cyclopropylmethanol (29µL, 0.366 mmol) in CH_2Cl_2 (5 mL) bis(trichloromethyl) carbonate (40 mg, 0.136 mmol) followed by DMAP (143 mg, 1.170 mmol) are added and the resulting milky suspension is stirred at RT for 15 min. Then a solution of ((3R*,4R*)-3-cyclopropylaminomethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (215 mg, 0.403 mmol) in CH_2Cl_2 (5 mL) is added and the resulting clear solution is stirred at RT for another 3.5 h. Evaporation of the solvent affords the crude product which is purified by preparative HPLC (Waters C_{18} ODB, eluent: H_2O/CH_3CN 20 to 100%) to give the title compound. MS (LC-MS): 532.0 $[M+H\text{-Boc}]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 6.48 min.

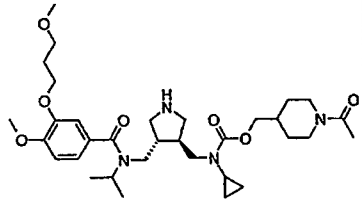
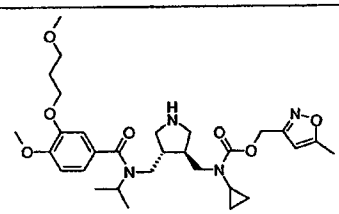
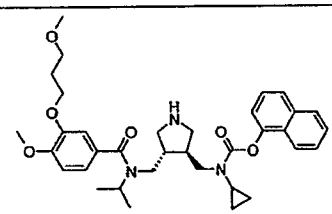
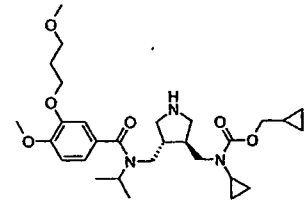
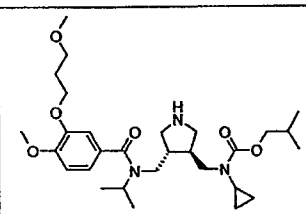
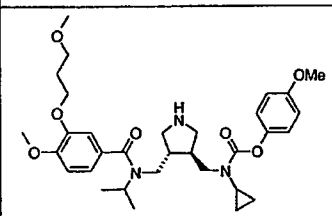
The following Examples are prepared according to the procedures described above for Example 233 or described below for Example 282:

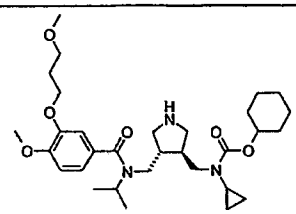
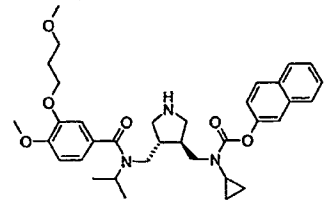
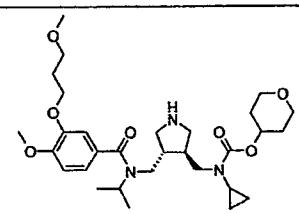
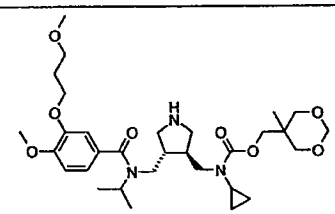
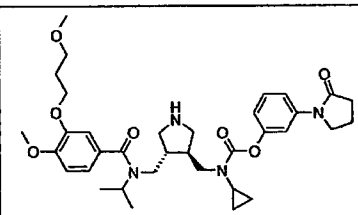
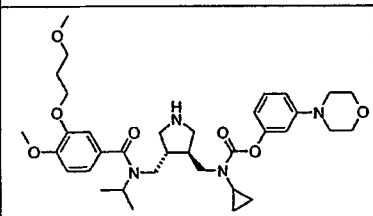
Table 9

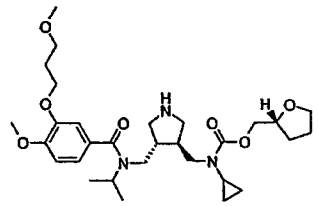
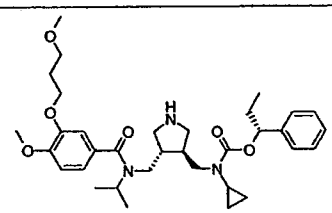
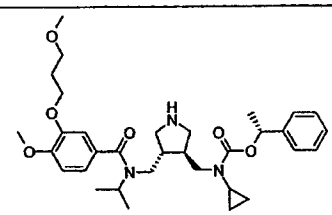
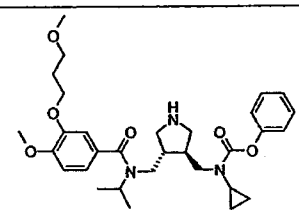
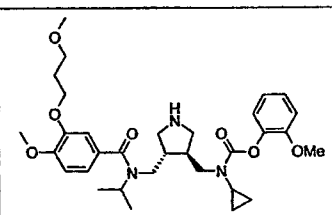
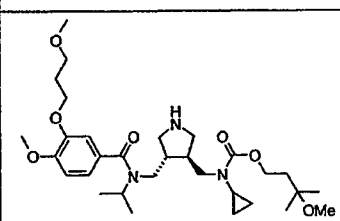
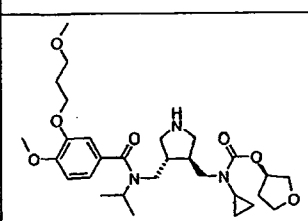
Example	configuration	structure	$[M+H]^+$	t_R (HPLC)
234	(3S*, 4S*)		568.0	5.27[a]

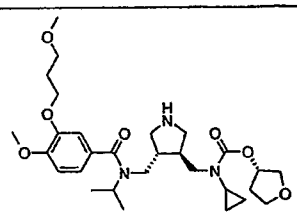
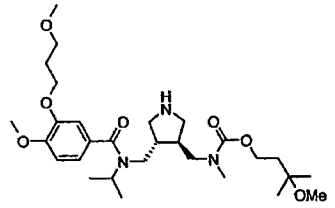
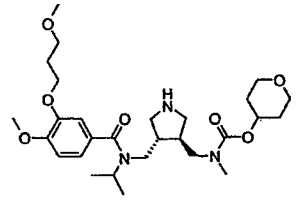
235	(3S, 4S)		568.2	5.17[a]
236	(3S*, 4S*)		534.1	5.35[a]
237	(3S*, 4S*)		285.1 $[M+2H]^{2+}$	4.70[a]
238	(3S*, 4S*)		295.1 $[M+2H]^{2+}$	4.72[a]
239	(3S*, 4S*)		536.0	5.10[a]
240	(3S*, 4S*)		576.1	5.25[a]

241	(3S*, 4S*)		548.1	5.83[a]
242	(3S*, 4S*)		546.1	4.76[a]
243	(3S*, 4S*)		591.4	4.25[a]
244	(3S*, 4S*)		554.3	4.70[a]
245	(3S*, 4S*)		591.4	4.19[a]
246	(3S*, 4S*)		617.4	4.41[a]

247	(3S*, 4S*)		617.5	4.26[a]
248	(3S*, 4S*)		573.4	4.54[a]
249	(3S*, 4S*)		604.2	5.14[a]
250	(3S, 4S)		532.3	4.87[a]
251	(3S, 4S)		534.2	5.11[a]
252	(3S, 4S)		584.2	5.69[a]

253	(3S, 4S)		560.2	5.92[a]
254	(3S, 4S)		604.2	6.01[a]
255	(3S, 4S)		562.3	5.42[a]
256	(3S, 4S)		592.3	5.58[a]
257	(3S, 4S)		637.5	5.88[a]
258	(3S, 4S)		639.2	5.90[a]

259	(3S, 4S)		562.5	5.41[a]
260	(3S, 4S)		596.0	6.35[a]
261	(3S, 4S)		582.0	5.03[a]
262	(3S, 4S)		554.0	4.83[a]
263	(3S, 4S)		584.0	4.85[a]
264	(3S, 4S)		578.5	3.36[b]
265	(3S, 4S)		548.5	3.08[b]

266	(3S, 4S)		548.4	0.38[b]
267	(3S, 4S)		552.2	4.44[a]
268	(3S, 4S)		536.2	2.58[c]

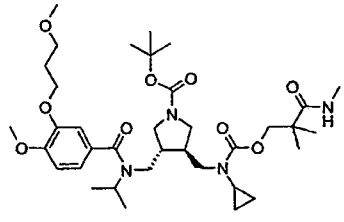
[a] t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min).

[b] t_R (Waters Symmetry C18 column, 10-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min).

[c] t_R (Waters Symmetry C18 column, 5-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min).

The starting material of Example 245 is prepared as follows:

(3S*,4R*)-3-{[Cyclopropyl-(2-methyl-2-methylcarbamoyl-propoxycarbonyl)-amino]-methyl}-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester



HBTU (161 mg, 0.43 mmol) is added to a solution of (3S*,4R*)-3-{[(2-carboxy-2-methyl-propoxycarbonyl)-cyclopropyl-amino]-methyl}-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (240 mg, 0.35

mmol) in CH_3CN (10 mL) at 0°C. After 5 min a solution of methylamine (44 µL, 0.35 mmol, 8M in EtOH) and triethylamine (493 µL, 3.54 mmol) in CH_3CN (10 mL) is added at 0°C and the reaction solution is stirred at RT for 5 h. Another portion of methylamine (0.22 mL, 1.75 mmol) is added and stirring is continued for another 16 h. Then, triethylamine (247 µL, 1.77 mmol) and HBTU (268 mg, 1.02 mmol) are added and the reaction mixture is stirred at 50°C for another 16 h. The solvent is evaporated and the crude product purified by HPLC (Interchrom C_{18} ODB 10 µm, 28x250 mm, eluent: CH_3CN/H_2O 5%/2.5 min, CH_3CN/H_2O 5-100%/23 min, 100% CH_3CN/4.5 min, flow 40 mL/min) to give the title compound. MS (LC-MS): 691.4 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.38 min.

The starting material is prepared as follows:

A. (3S*,4R*)-3-{[Cyclopropyl-(2-methoxycarbonyl-2-methyl-propoxycarbonyl)-amino]-methyl}-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound is prepared analogously as described above for NVP-BGW706 from ((3R*,4R*)-3-cyclopropylaminomethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester and methyl 2,2-dimethyl-3-hydroxypropionate using bis(trichloromethyl) carbonate. MS (LC-MS): 592.1 $[M+H\text{-}Boc]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.92 min.

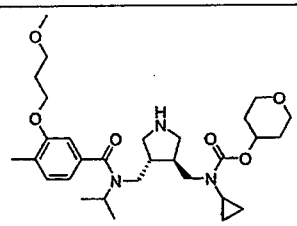
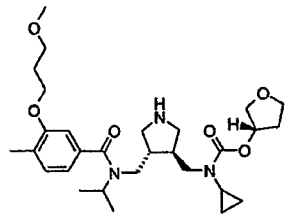
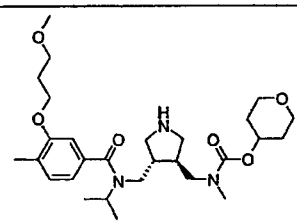
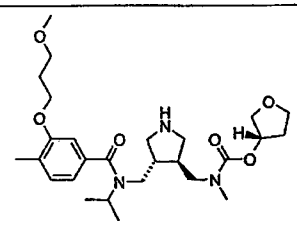
B. (3S*,4R*)-3-{[(2-Carboxy-2-methyl-propoxycarbonyl)-cyclopropyl-amino]-methyl}-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

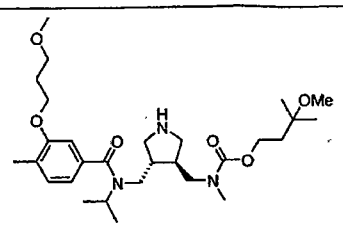
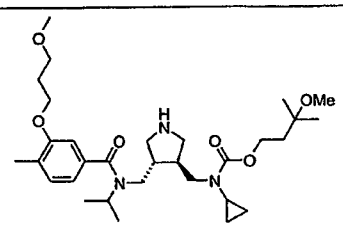
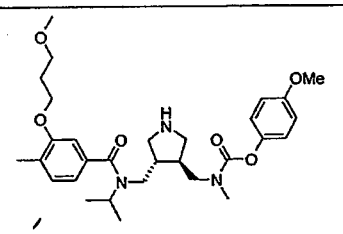
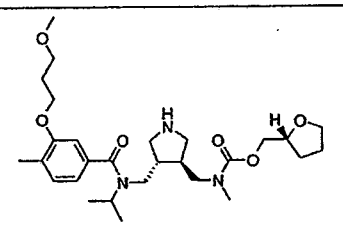
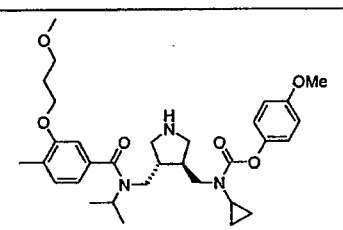
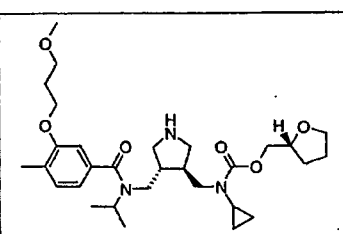
A mixture of (3S*,4R*)-3-{[cyclopropyl-(2-methoxycarbonyl-2-methyl-propoxycarbonyl)-amino]-methyl}-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (290 mg, 0.42 mmol) and $LiOH\bullet.H_2O$ (44 mg, 1.05 mmol) in H_2O (2 mL) and THF (6 mL) is stirred at RT for 3 d. After evaporation of the solvent 1N HCl is added and the mixture is extracted with ethyl acetate. Drying (Na_2SO_4) of the combined extracts, filtration and evaporation of the solvent affords the title compound which is used without further purification. MS (LC-MS): 578.0 $[M+H\text{-}Boc]^+$; t_R (HPLC,

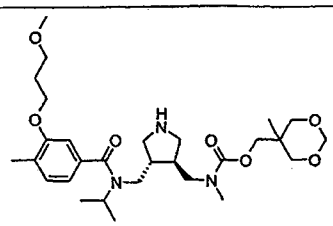
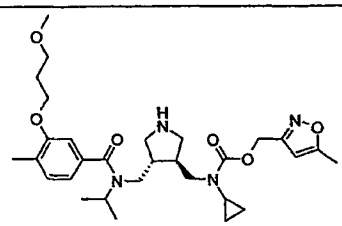
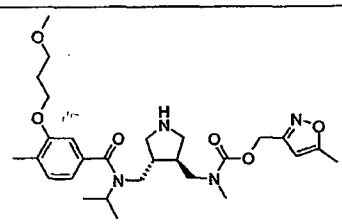
Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.44 min.

The following Examples are prepared according to the procedures described above for Example 233 or below for Example 282 using (3R,4R)-3-cyclopropylaminomethyl-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester or (3R,4R)-3-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-4-methylaminomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester:

Table 10

Example	configuration	structure	$[M+H]^+$	t_R (HPLC)
269	(3S, 4S)		546.3	5.76[a]
270	(3S, 4S)		532.3	4.71[a]
271	(3S, 4S)		520.3	4.57[a]
272	(3S, 4S)		506.2	4.52[a]

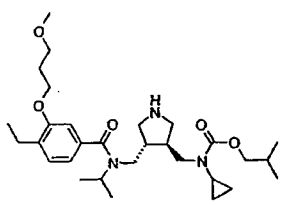
273	(3S, 4S)		536.3	2.64[b]
274	(3S, 4S)		562.3	5.03[a]
275	(3S, 4S)		542.2	5.00[a]
276	(3S, 4S)		520.3	4.67[a]
277	(3S, 4S)		568.3	5.18[a]
278	(3S, 4S)		546.3	4.85[a]

279	(3S, 4S)		550.3	4.74[a]
280	(3S, 4S)		557.2	2.68[b]
281	(3S, 4S)		531.1	2.51[b]

[a] t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min).

[b] t_R (Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min).

Example 282 : Cyclopropyl-[(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid isobutyl ester



To a solution of (3S,4R)-3-[(cyclopropyl-isobutoxycarbonyl-amino)-methyl]-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.280 g, 0.443 mmol) in dioxane (2 mL), 4N HCl in dioxane (2 mL) is added, and the resulting solution is lyophilized to afford the corresponding hydrochloride salt. MS (LC-MS): 532 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.52 min.

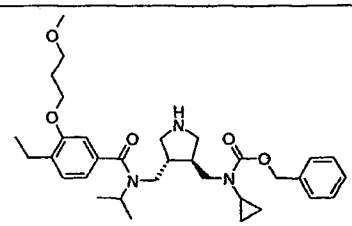
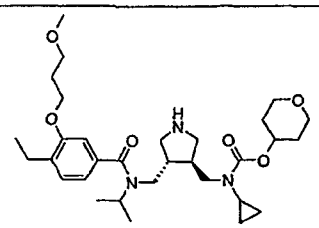
The starting material is prepared as follows:

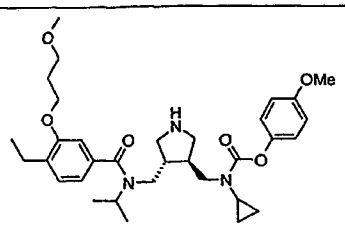
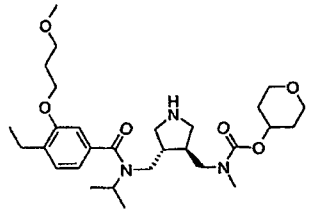
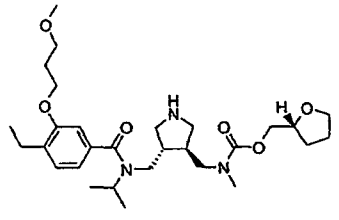
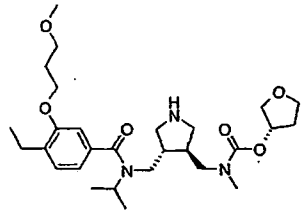
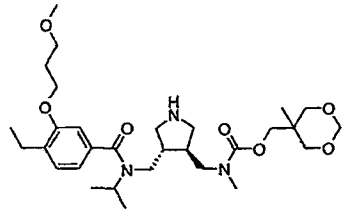
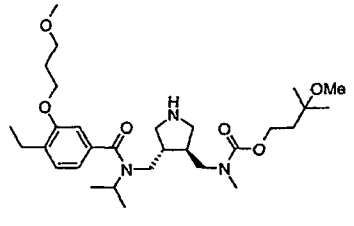
(3S,4R)-3-[(Cyclopropyl-isobutoxycarbonyl-amino)-methyl]-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (3R,4R)-3-cyclopropylaminomethyl-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (250 mg, 0.470 mmol) in CH_2Cl_2 (3 mL) are added isobutylchloroformate (84 mg, 0.611 mmol) and triethylamine (85 µL, 0.611 mmol) under a N_2 atmosphere. The mixture is stirred overnight at RT, diluted with CH_2Cl_2 and poured into an aqueous saturated solution of $NaHCO_3$. The layers are separated and the aqueous one extracted twice with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude residue is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 100:0 to 90:10) to give the title compound. MS (LC-MS): 532 $[M+H\text{-}Boc]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 8.22 min.

The following Examples are prepared according to the procedures described above for Example 233 or Example 282:

Table 11

Example	configuration	structure	$[M+H]^+$	t_R (HPLC)
283	(3S, 4S)		556	5.53[a]
284	(3S, 4S)		560.3	2.68[b]

285	(3S, 4S)		582.2	2.95[b]
286	(3S, 4S)		534.2	4.80[a]
287	(3S, 4S)		534.2	4.87[a]
288	(3S, 4S)		520.3	4.73[a]
289	(3S, 4S)		564.3	4.91[a]
290	(3S, 4S)		550.2	2.80[b]

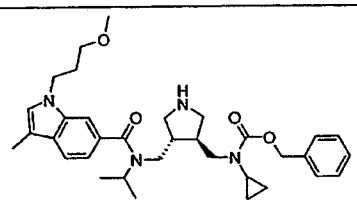
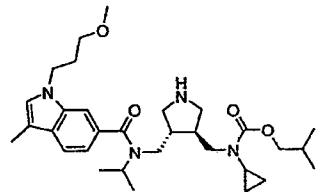
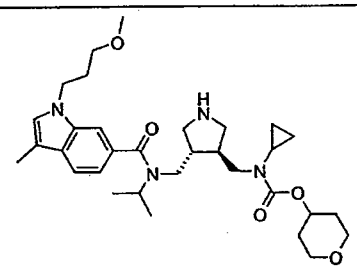
[a] t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min).

240

[b] t_R (Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min).

The following Examples are prepared according to the procedures described above for Example 233 or Example 282 using (3R,4R)-3-cyclopropylaminomethyl-4-({isopropyl-[1-(3-methoxy-propyl)-3-methyl-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester:

Table 12

Example	configuration	structure	$[M+H]^+$	t_R (HPLC)
291	(3S, 4S)		575	5.67[a]
292	(3S, 4S)		541	5.66[a]
293	(3S, 4S)		569.3	4.22[b]

[a] t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min).

[b] t_R (HPLC, Nucleosil C-18HD (4x70mm, 3µm), 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/ 1.5 min; flow: 1 mL/min).

N-(2-Hydroxy-1,1-dimethyl-ethyl)-acetamide

A mixture of 2-amino-2-methyl-propan-1-ol (2.0 mL, 20.4 mmol), acetanhydride (1.9 mL, 20.4 mmol) and $NaHCO_3$ (2.6 g, 30.6 mmol) in H_2O (20 mL) is stirred at RT for 16 h. For

workup 1N HCl is added and the mixture is extracted with ethyl acetate. Drying (Na_2SO_4) of the combined extracts, filtration and evaporation of the solvent yields the title compound as a colorless solid. MS (LC-MS): $[M+H]^+$= 132.2. t_R (HPLC, Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min): 0.38 min.

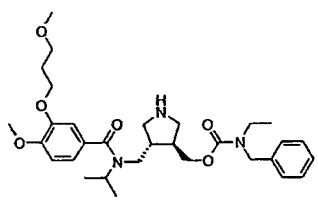
N-(1-Hydroxymethyl-cyclopentyl)-acetamide

The title compound is prepared analogously as described for N-(2-hydroxy-1,1-dimethyl-ethyl)-acetamide from (1-amino-cyclopentyl)-methanol. MS (LC-MS): $[M+H]^+$= 158.2. t_R (HPLC, Waters sun fire C18 column, 5-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.8 mL/min): 1.76 min.

1-(4-Hydroxymethyl-piperidin-1-yl)-ethanone

The title compound is prepared analogously as described for N-(2-hydroxy-1,1-dimethyl-ethyl)-acetamide from piperidin-4-yl-methanol. MS (LC-MS): $[M+H]^+$= 158.3. t_R (HPLC, Waters Symmetry C18 column, 5-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min): 0.39 min.

Example 294 : Benzyl-ethyl-carbamic acid (3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl ester



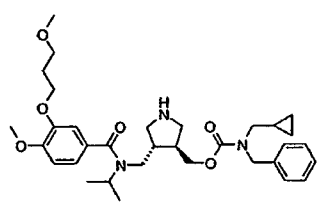
To a solution of (3S,4R)-3-[(benzyl-ethyl-carbamoyloxy)-methyl]-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (83 mg, 0.127 mmol) in 2 mL dioxane, 4 N HCl in dioxane (1 mL, 4 mmol) is added. The mixture is stirred at RT for 2 h, and the resulting solution is lyophilized to afford the corresponding hydrochloride salt. MS (LC-MS): 556.1 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.89 min.

The starting material is prepared as follows:

(3S,4R)-3-[(Benzyl-ethyl-carbamoyloxy)-methyl]-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

To a stirred solution of (3S,4R)-3-hydroxymethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (250 mg, 0.505 mmol) in CH_2Cl_2 (10 mL) is added triphosgen (56 mg, 0.187 mmol) and DMAP (197 mg, 1.62 mmol). The resulting solution is stirred 30 min before the addition of commercially available N-ethylbenzylamine (113 µL, 0.758 mmol). The mixture is further stirred overnight, then diluted with CH_2Cl_2 and poured into an aqueous saturated solution of $NaHCO_3$. The layers are separated and the aqueous one extracted twice with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude material is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 100:0 to 98:2). TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.2. MS (LC-MS): 655.9 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 6.36 min.

Example 295 : Benzyl-cyclopropylmethyl-carbamic acid (3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl ester



The title compound is prepared analogously as described in Example 294 from (3S,4R)-3-hydroxymethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester and benzyl-cyclopropylmethyl-amine. MS (LC-MS): 582.0 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 5.15 min.

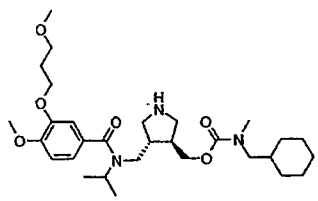
The starting material is prepared as follows:

Benzyl-cyclopropylmethyl-amine

A mixture of benzaldehyde (3 mL, 29.55 mmol), cyclopropanemethylamine (2.53 mL, 29.55 mmol), AcOH (1.7 mL, 29.55 mmol) in 1,2-dichloroethane (150 mL) is stirred at RT for 25 minutes. Sodium triacetoxyborohydride (8.8 g, 41.37 mmol) is added and the mixture further

stirred overnight at RT. Sodium triacetoxyborohydride (3.13 g, 15 mmol) is again added to complete the reaction. The mixture is quenched by the addition of NaOH 1N (50 mL), the layers are separated and the aqueous phase is extracted twice with ether. The combined organic extracts are dried (Na_2SO_4), filtered and concentrated. The crude material is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 95:5 to 80:20+ 5% NH_3) to give the title product. t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.91 min.

Example 296: Cyclohexylmethyl-methylcarbamic acid (3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxypropoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-yl-methyl ester



To a solution of (3S,4R)-3-[(cyclohexylmethyl-methyl-carbamoyloxy)-methyl]-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (182 mg, 0.281 mmol) in 1 mL dioxane, 4 N HCl in dioxane (2 mL, 8 mmol) is added. The mixture is stirred at RT for 2 h, and the resulting solution is lyophilized to afford the corresponding hydrochloride salt. MS (LC-MS): 548 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 5.14 min.

The starting material is prepared as follows:

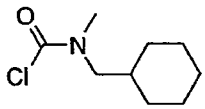
(3S,4R)-3-[(cyclohexylmethyl-methyl-carbamoyloxy)-methyl]-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

To a stirred suspension of NaH (60% oily dispersion, 17 mg, 0.42 mmol) in THF (2 mL) is added at 0°C (3S,4R)-3-hydroxymethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (160 mg, 0.303 mmol) in THF (3 mL). The resulting solution is stirred 30 min before the addition of a solution of cyclohexylmethyl-methyl-carbamoyl chloride (80 mg, 0.421 mmol) in THF (3 mL). The mixture is further stirred overnight at RT and poured into an aqueous solution of NH_4Cl.

AcOEt is added, the layers are separated and the aqueous one extracted twice with AcOEt. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude material is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 100:0 to 95:5). TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.25. MS (LC-MS): 648 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 6.83 min.

Intermediates are prepared as described by the following methods:

Cyclohexylmethyl-methyl-carbamoyl chloride



a. Cyclohexylmethyl-methyl-amine

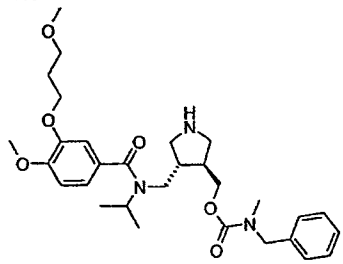
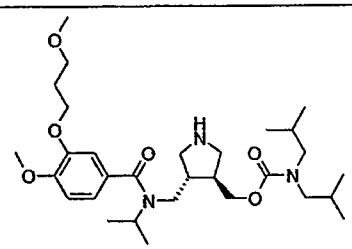
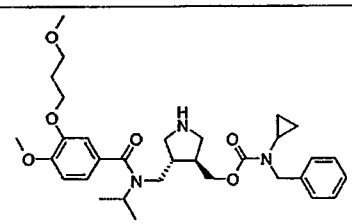
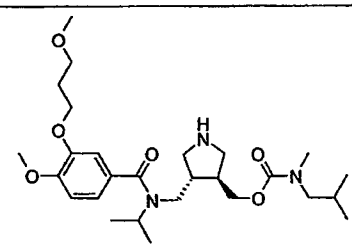
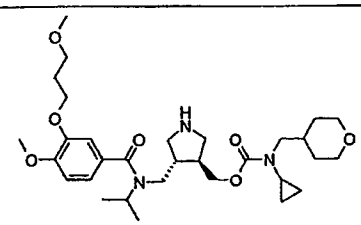
A solution of cyclohexancarbaldehyde (4 mL, 33.24 mmol) and methylamine (50.0 mL, 99.8 mmol) in MeOH (160 mL containing 2% AcOH) is stirred at RT for 1 h. Sodium borohydride (2.515 g, 66.48 mmol) is added portionwise at 0°C and stirring is continued, at RT for 1 h. A solution of NaOH 1N is added and the methanol is concentrated. CH_2Cl_2 is added, the layers are separated and the aqueous one extracted twice with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude material is purified by flash chromatography (eluent: CH_2Cl_2/MeOH 95:5 to 80:20+ 5% NH_3) to give the title product. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.1; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, flow: 1.5 ml/min): 7.09 min.

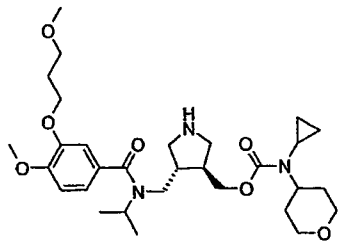
b. Cyclohexylmethyl-methyl-carbamoyl chloride

To a solution of triphosgene (77 mg, 0.259 mmol) in CH_2Cl_2 (1 mL) at - 78°C is added dropwise pyridine (63 µl, 0.786 mmol) followed by a solution of cyclohexylmethyl-methyl-amine (100 mg, 0.786 mmol) in CH_2Cl_2 (1 mL). The yellow mixture is allowed to reach RT and stirred overnight. The solvent is concentrated, and the residue taken up in AcOEt. An aqueous saturated solution of $NaHCO_3$ is added, the layers are separated and the aqueous one is extracted twice with AcOEt. The combined organic extracts are washed with brine, dried over Na_2SO_4, filtered and concentrated to afford the title compound as a yellow oil. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.95. MS (LC-MS): 189.1 $[M+H]^+$.

The following Examples are prepared according to the procedures described above for Example 296 :

Table 13

Example	configuration	structure	$[M+H]^+$	t_R (HPLC)
297	(3S*, 4S*)		542.5	4.70[a]
298	(3S, 4S)		550	5.33[a]
299	(3S, 4S)		568	4.15[a]
300	(3S, 4S)		508	5.13[a]
301	(3S, 4S)		576.3	4.44[a]

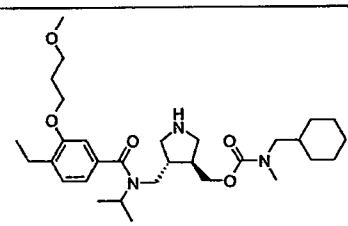
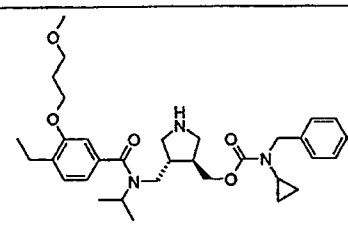
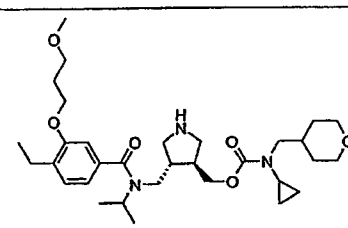
302	(3S, 4S)		562.3	1.07[b]

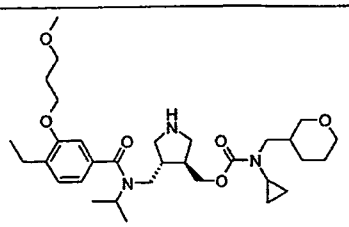
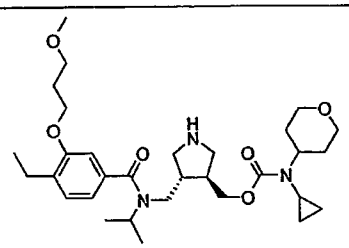
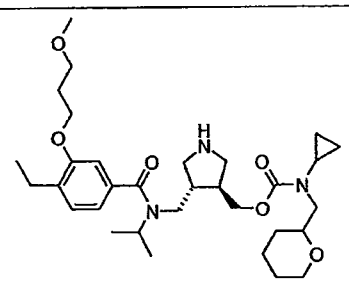
[a] t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min).

[b] t_R (HPLC Zorbax SB C18, 10-95% CH_3CN/H_2O/0.8 min, 95% CH_3CN/0.7 min, CH_3CN and H_2O containing 0.1% HCOOH, flow: 1.5 ml/min).

The following Examples are prepared according to the procedures described above for Example 296 using (3R,4S)-3-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-4-hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester:

Table 14

Example	configuration	structure	$[M+H]^+$	t_R (HPLC)
303	(3S, 4S)		546.6	5.41[b]
304	(3S, 4S)		566.6	5.10[b]
305	(3S, 4S)		574.4	5.02[a]

306	(3S, 4S)		574.2	5.04[b] 5.13[b]
307	(3S, 4S)		560.3	4.94[a]
308	(3S, 4S)		574.2	4.87[b]

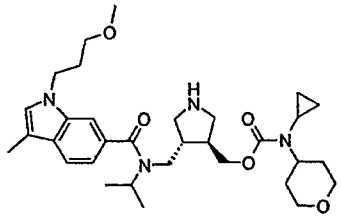
[a] t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min). ou 1.5 de flux attendre reponse anne

[b] t_R (HPLC, Nucleosil C18-HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/1.5 min, flow: 1 ml/min).

The following Examples are prepared according to the procedures described above for Example 296 starting from (3S,4R)-3-hydroxymethyl-4-({isopropyl-[1-(3-methoxy-propyl)-3-methyl-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester:

Table 15

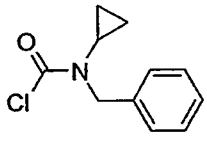
Example	configuration	structure	$[M+H]^+$	t_R (HPLC)

309	(3S, 4S)		569.3	2.39

t_R (HPLC, Waters Symmetry C18 column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/1.5 min).

Intermediates are prepared as described by the following methods:

Benzyl-cyclopropyl-carbamoyl chloride



a. Benzyl-cyclopropyl-amine

The title compound is prepared analogously as described for benzyl-cyclopropylmethyl-amine. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.1, MS (LC-MS): 148.2 $[M+H]^+$.

b. Benzyl-cyclopropyl-carbamoyl chloride

The title compound is prepared analogously as described for cyclohexylmethyl-methyl-carbamoyl chloride. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.9. MS (LC-MS): $[M+H]^+$= 210.2. t_R (HPLC, Waters Symmetry C18 column, 20-100% CH_3CN/H_2O/5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min): 4.67 min.

Cyclopropyl-(tetrahydro-pyran-4-ylmethyl)-carbamoyl chloride

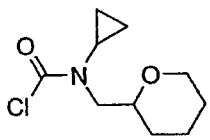
The title compound is prepared analogously as described for benzyl-cyclopropyl-carbamoyl chloride starting from cyclopropyl-(tetrahydro-pyran-4-ylmethyl)-amine (prepared analogously as described for benzyl-cyclopropylmethyl-amine). TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.9.

Cyclopropyl-(tetrahydro-pyran-3-ylmethyl)-carbamoyl chloride

The title compound is prepared analogously as described for benzyl-cyclopropyl-carbamoyl chloride starting from cyclopropyl-(tetrahydro-pyran-3-ylmethyl)-amine (prepared

analogously as described for benzyl-cyclopropylmethyl-amine). TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.9.

Cyclopropyl-(tetrahydro-pyran-2-ylmethyl)-carbamoyl chloride



a. Toluene-4-sulfonic acid tetrahydro-pyran-2-ylmethyl ester

To a suspension of tetrahydropyran-2-methanol (2 g, 17.2 mmol) cooled at 0°C is added toluene-4-sulfonyl chloride (3.6 g, 18.92 mmol), followed by (2.63 mL , 18.92 mmol) of triethylamine. The mixture is allowed to reach RT and stirred overnight. Then poured into an aqueous saturated solution of $NaHCO_3$. The layers are separated and the aqueous one extracted twice with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude material is purified by flash chromatography on silica gel (eluent: c-hexane/AcOEt 80:20) to give the title product. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.9. MS (LC-MS): 271.1 $[M+H]^+$, t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, flow: 1.5 ml/min): 5.32 min.

b. Cyclopropyl-(tetrahydro-pyran-2-ylmethyl)-amine

A mixture of toluene-4-sulfonic acid tetrahydro-pyran-2-ylmethyl ester (500 mg, 1.85 mmol) and cyclopropylamine (2 mL, 15 mmol) is heated overnight at 110 °C in a sealed tube. The crude mixture is concentrated and taken up in CH_2Cl_2. Water is added, the layers are separated and the aqueous one back extracted twice with CH_2Cl_2. The combined organic extracts are washed with brine, dried over Na_2SO_4, filtered and concentrated. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.3, MS (LC-MS): 156.2 $[M+H]^+$.

c. Cyclopropyl-(tetrahydro-pyran-2-ylmethyl)-carbamoyl chloride

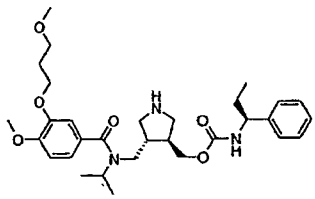
To a stirred solution of cyclopropyl-(tetrahydro-pyran-2-ylmethyl)-amine (200 mg, 0.74 mmol) in THF (4 mL) is added triethylamine (144 µL, 1.036 mmol) and 4-dimethylaminopyridine (1.81 mg, 0.015 mmol). The mixture is cooled to 0°C, and triphosgene (88 mg, 0.296 mmol) is added in one portion. After stirring for 30 min at 0°C and overnight at RT, water is cautiously added and the solution is extracted with AcOEt. The combined organic extracts

are washed with brine, dried over Na_2SO_4, filtered and concentrated. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.9.

Cyclopropyl-(tetrahydro-pyran-4-yl)-carbamoyl chloride

The title compound is prepared analogously as described for cyclopropyl-(tetrahydro-pyran-2-ylmethyl)-carbamoyl chloride starting from commercially available cyclopropyl-(tetrahydro-pyran-4-yl)-amine. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.9.

Example 310 : ((S)-1-Phenyl-propyl)-carbamic acid (3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl ester



To a solution of (3R,4S)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-((S)-1-phenyl-propylcarbamoyloxymethyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (49 mg, 0.075 mmol) in 1 mL dioxane, 4 N HCl in dioxane (0.5 mL, 2 mmol) is added. The mixture is stirred at RT for 2 h, and the resulting solution is lyophilized to afford the corresponding hydrochloride salt. MS (LC-MS): 556.3 $[M+H]^+$; t_R (HPLC, Nucleosil C18-HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/1.5 min, flow: 1 ml/min): 4.11 min.

The starting material is prepared as follows:

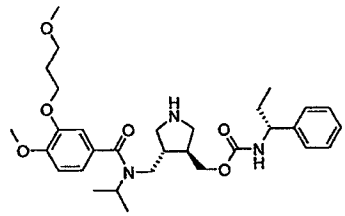
(3R,4S)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-((S)-1-phenyl-propylcarbamoyloxymethyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (3S,4R)-3-hydroxymethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (200 mg, 0.404 mmol) in ether (12 mL) are successively added (S)-1-phenylpropyl isocyanate (130.4 mg, 0.809 mmol) and $AlCl_3$ (54 mg, 0.404 mmol). The mixture is stirred at RT under nitrogen overnight. (S)-1-phenylpropyl isocyanate (150 µL) and $AlCl_3$ (54 mg, 0.404 mmol) are again added and the mixture further stirred for 5 h. AcOEt is added and the reaction mixture quenched by the addition of an aqueous saturated solution of $NaHCO_3$. The layers are separated and the aqueous one back extracted twice with AcOEt. The combined organic extracts are dried over

Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 100:0 to 95:5) to give the title product TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.35. MS (LC-MS): 656.2 $[M+H]^+$; t_R (HPLC, Nucleosil C18-HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/1.5 min, flow: 1 ml/min): 3.94 min.

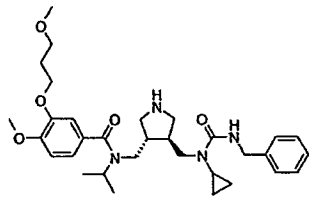
The following Examples are prepared according to the procedures described above for Example 310 :

Table 16

Example	configuration	structure	$[M+H]^+$	t_R (HPLC)
311	(3S, 4S)		556.3	4.13

t_R (HPLC, Nucleosil C18-HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/1.5 min, flow: 1 ml/min).

Example 312: N-[(3S*,4S*)-4-(3-Benzyl-1-cyclopropyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

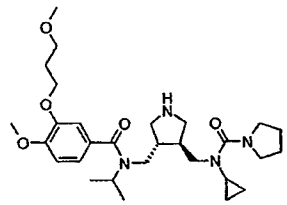


To a solution of (3R*,4R*)-3-(3-benzyl-1-cyclopropyl-ureidomethyl)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (270 mg, 0.405 mmol) in dioxane (5 mL), 4N HCl in dioxane (3 mL) is added and the resulting solution is stirred at RT for 5 h. Lyophilization affords the corresponding hydrochloride salt as a colorless powder. MS (LC-MS): 567.0 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.18 min.

The starting material is prepared as follows:

(3R*,4R*)-3-(3-Benzyl-1-cyclopropyl-ureidomethyl)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester To a solution of ((3R*,4R*)-3-cyclopropylaminomethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (235 mg, 0.440 mmol) in THF (6 mL) is added triethylamine (123 µL, 0.880 mmol) followed by benzylisocyanate (54 µL, 0.440 mmol). The mixture is stirred at RT for 2 h before water is added. Extraction with ethyl acetate, drying of the combined extracts (Na_2SO_4), filtration and evaporation of the solvent affords the crude product which is purified by flash chromatography on silica gel (eluent gradient: CH_2Cl_2 100% to CH_2Cl_2/MeOH 9:1) to give the title compound. MS (LC-MS): 667.1M+H]$^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 6.26 min.

Example 313: Pyrrolidine-1-carboxylic acid cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide



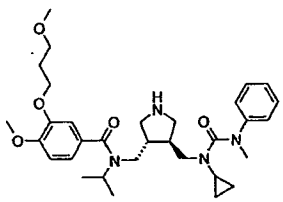
To a solution of (3R*,4R*)-3-{[cyclopropyl-(pyrrolidine-1-carbonyl)-amino]-methyl}-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (165 mg, 0.262 mmol) in dioxane (5 mL), 4N HCl in dioxane (3 mL) is added and the resulting solution is stirred at RT for 4.5 h. Lyophilization affords the corresponding hydrochloride salt as a colorless solid. MS (LC-MS): 531.1 [M+H]$^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.11 min.

The starting material is prepared as follows:

(3R*,4R*)-3-{[Cyclopropyl-(pyrrolidine-1-carbonyl)-amino]-methyl}-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

Triethylamine (99 µL, 0.714 mmol) followed by 1-pyrrolidinecarbonyl chloride is added to a solution of ((3R*,4R*)-3-cyclopropylaminomethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (254 mg, 0.476 mmol) in CH_2Cl_2 (20 mL). The resulting solution is stirred at RT for 2 h and at 60°C for another 24 h. Evaporation of the solvent affords the crude product which is purified by preparative HPLC (Waters C_{18} ODB, eluent: H_2O/CH_3CN 20 to 100%) to give the title compound. MS (LC-MS): 631.1 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 6.31 min.

Example 314: N-[(3S*,4S*)-4-(1-Cyclopropyl-3-methyl-3-phenyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide



A solution of (3R*,4R*)-3-(1-cyclopropyl-3-methyl-3-phenyl-ureidomethyl)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (195 mg, 0.29 mmol) in 4N HCl/dioxane (8 mL) is stirred at RT until the reaction is complete. Lyophilization affords the title compound as a colorless foam. MS (LC-MS): 567.1 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 4.57 min.

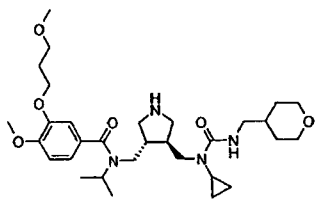
The starting material is prepared as follows:

(3R*,4R*)-3-(1-Cyclopropyl-3-methyl-3-phenyl-ureidomethyl)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

A mixture of (3R*,4R*)-3-cyclopropylaminomethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (216 mg, 0.41 mmol), N-methyl-N-phenyl carbamoylchloride (274 mg, 1.62 mmol), triethylamine (0.45 mL,

3.24 mmol) and DMAP (1 mg, 0.008 mmol) in THF (15 mL) is heated at 60°C for 4 h. After cooling to RT 1N HCl is added and the mixture is extracted with ethyl acetate, the combined organic extracts are dried (Na_2SO_4), filtered and the solvent is evaporated. Purification by flash chromatography on silica gel (eluent gradient: CH_2Cl_2 100% CH_2Cl_2/MeOH 9:1) affords the title compound. MS (LC-MS): 667.1 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 6.02 min.

Example 315 N-{(3S,4S)-4-[1-Cyclopropyl-3-(tetrahydro-pyran-4-ylmethyl)-ureido-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy) -benzamide



To a solution of (3R*,4R*)-3-[1-cyclopropyl-3-(tetrahydro-pyran-4-ylmethyl)-ureidomethyl]-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (50 mg, 0.074 mmol) in dioxane (3 mL), 4N HCl in dioxane (1 mL) is added and the resulting solution is stirred at RT for 5 h. Lyophilization affords the corresponding hydrochloride salt as a colorless solid. MS (LC-MS): 575.1 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.29 min.

The starting material is prepared as follows:

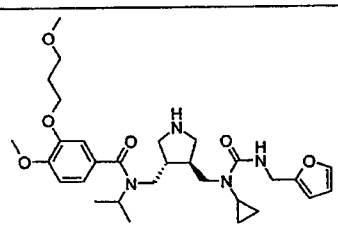
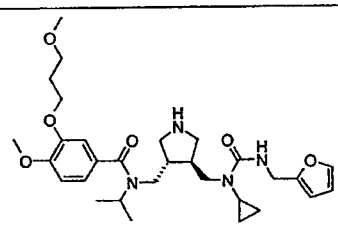
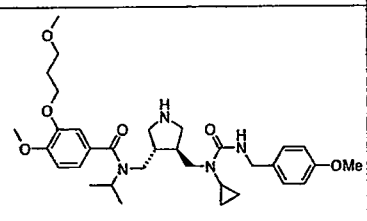
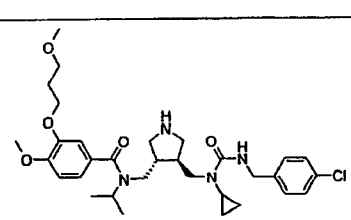
(3R*,4R*)-3-[1-Cyclopropyl-3-(tetrahydro-pyran-4-ylmethyl)-ureidomethyl]-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

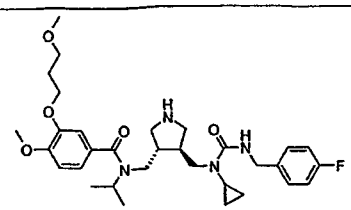
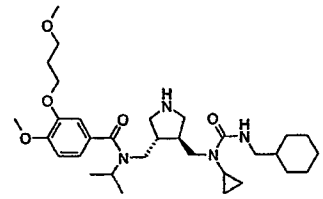
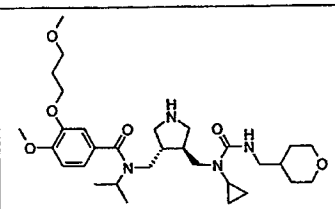
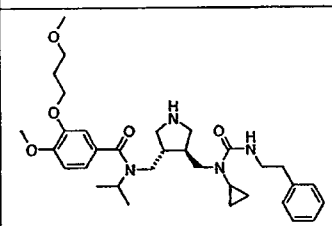
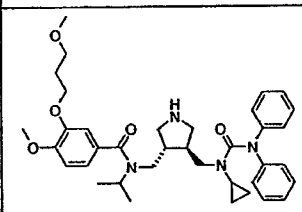
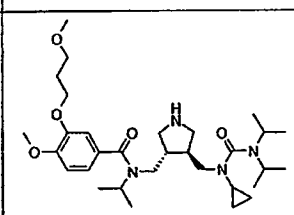
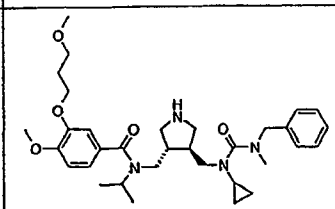
4-Aminomethyl tetrahydropyrane (50 mg, 0.435 mmol) is added to a suspension of bis(trichloromethyl) carbonate (155 mg, 0.522 mmol) and charcoal (10 mg) in AcOEt(8 mL) at RT. The mixture is stirred at RT for 5 min and heated under reflux for another 10 min before it is allowed to cool to RT. Filtration and evaporation of the solvent affords the corresponding isocyanate which is used without further purification and dissolved in CH_3CN (10 mL). ((3R*,4R*)-3-Cyclopropylaminomethyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-

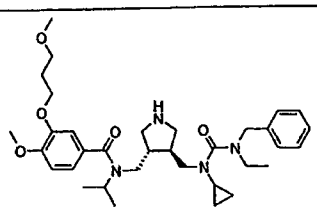
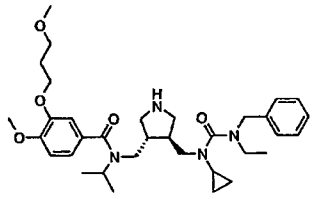
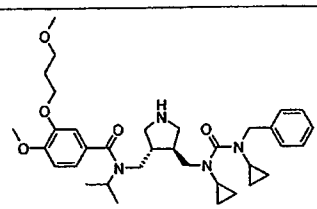
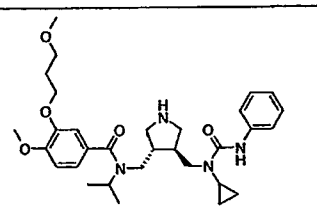
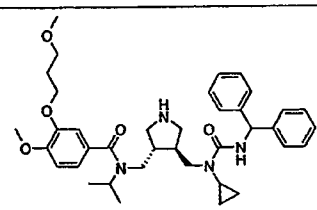
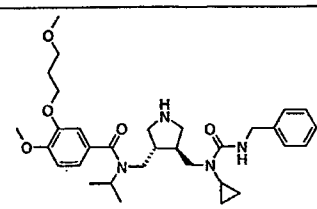
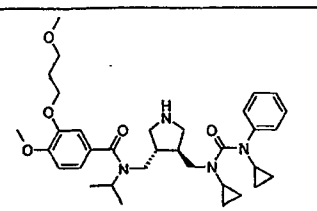
propoxy)-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (232 mg, 0.435 mmol) is added and the mixture is heated under reflux for 16 h. For workup the solvent is evaporated and purified by preparative HPLC (Interchrom C_{18} ODB, eluent: CH_3CN/H_2O 5%/2.5 min, CH_3CN/H_2O 5-100%/22.5 min, 100% CH_3CN/4.5 min, flow 40 mL/min) to give the title compound. MS (LC-MS): 675.1 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 6.19 min.

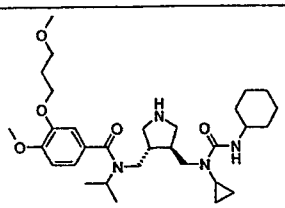
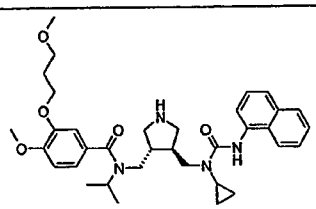
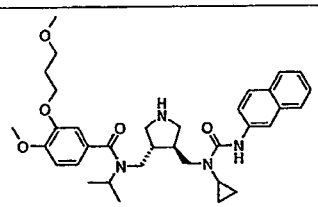
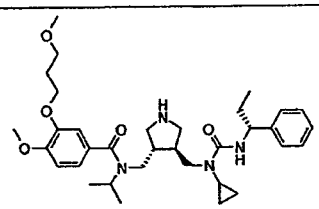
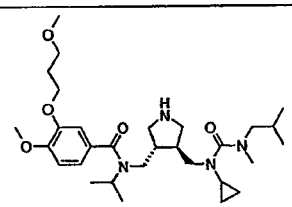
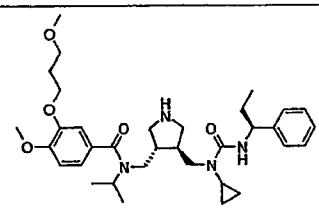
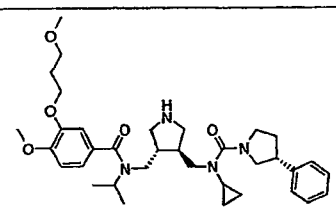
The following Examples are prepared according to the procedures described above for Example 312 or Example 314:

Table 17

Example	configuration	structure	$[M+H]^+$	t_R (HPLC)
316	(3S*, 4S*)		557.0	5.17[a]
317	(3S, 4S)		557.5	4.77[a]
318	(3S*, 4S*)		597.1	5.35[a]
319	(3S*, 4S*)		601.0	5.58[a]

320	(3S*, 4S*)		585.0	5.42[a]
321	(3S*, 4S*)		573.1	5.73[a]
322	(3S*, 4S*)		575.1	5.29[a]
323	(3S*, 4S*)		581.1	5.67[a]
324	(3S*, 4S*)		629.1	5.85[a]
325	(3S*, 4S*)		561.1	5.70[a]
326	(3S*, 4S*)		581.1	4.66[a]

327	(3S*, 4S*)		595.1	4.78[a]
328	(3S, 4S)		595.0	5.04[a]
329	(3S*, 4S*)		607.5	4.96[a]
330	(3S*, 4S*)		553.3	4.74[a]
331	(3S*, 4S*)		643.2	5.17[a]
332	(3S, 4S)		567.3	4.82[a]
333	(3S*, 4S*)		593.3	4.94[a]

334	(3S*, 4S*)		559.5	5.05[a]
335	(3S*, 4S*)		603.3	5.52[a]
336	(3S, 4S)		603.3	5.95[a]
337	(3S, 4S)		595.2	5.85[a]
338	(3S, 4S)		547.2	5.91[a]
339	(3S, 4S)		595.2	5.13[a]
340	(3S, 4S)		607.5	3.47[b]

260

[a] t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min).
[b] t_R (HPLC, Waters Symmetry C18 column, 10-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min).

Benzyl-methyl-carbamoyl chloride

At -78°C pyridine (1.25 mL, 15.5 mmol) followed by methyl benzylamine (2.0 mL, 15.5. mmol) are added to a solution of bis(trichloromethyl) carbonate (1.55 g, 5.2 mmol) in CH_2Cl_2 (20 mL). The reaction mixture is allowed to warm to RT and stirred for another 1.5 h. For workup 1N HCl is added to the yellow suspension and the mixture is extracted with ethyl acetate. Drying (Na_2SO_4) of the combined organic exctracts, filtration and evaporation of the solvent affords the title compound. MS (LC-MS): $[M+H]^+$= 184.1. t_R (HPLC, Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min): 3.84 min.

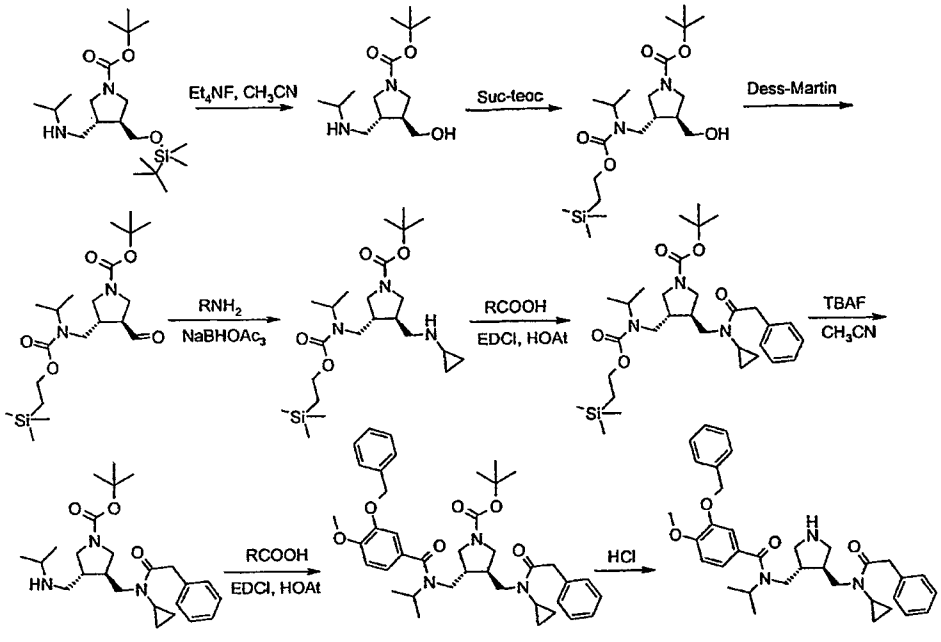
Benzyl-ethyl-carbamoyl chloride

The title compound is prepared analogously as described for benzyl-methyl-carbamoyl chloride from benzyl ethylamine. MS (LC-MS): $[M+H]^+$= 198.1. t_R (HPLC, Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min): 4.12 min.

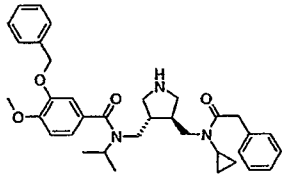
Phenyl-cyclopropyl-carbamoyl chloride

The title compound is prepared analogously as described for benzyl-methyl-carbamoyl chloride from cyclopropyl-phenyl-amine prepared according to Synlett **2003**, *14*, 2139. MS (LC-MS): $[M+H]^+$= 196.2. t_R (HPLC, Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min): 4.44 min.

Scheme 6



Example 341: 3-Benzyloxy-N-{(3S,4S)-4-[(cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-benzamide



To a solution of (3R,4R)-3-{[(3-benzyloxy-4-methoxy-benzoyl)-isopropyl-amino]-methyl}-4-[(cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester (0.191 g, 0.285 mmol) in dioxane (2 mL), 4N HCl in dioxane (1.07 mL) is added, and the resulting solution is stirred for 2 h, then lyophilized to afford the corresponding hydrochloride salt. MS (LC-MS): 570.2 $[M+H]^+$; t_R (HPLC, C18 column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/1.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.60 min.

The starting material is prepared as follows:

A. (3S,4R)-3-Hydroxymethyl-4-(isopropylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (3S,4R)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-(isopropylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (prepared under F in Example 9, Scheme 5) (19.5 g, 47.4 mmol) in MeCN (250 ml) is added Et_4NF (14.4 g, 94.8 mmol) and the resulting is refluxed for 3 h. The solvent is concentrated under reduced pressure and the crude material is taken up in AcOEt, a saturated aqueous solution of $NaHCO_3$ is added and the layers are separated. The aqueous layer is back extracted twice with AcOEt and the combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The compound was used in the next step without further purification. TLC, R_f ($MeOH/CH_2Cl_2$ 1:9): 0.22. MS (LC-MS): 273.0 $[M+H]^+$.

B. (3S,4S)-3-Hydroxymethyl-4-{[isopropyl-(2-trimethylsilanyl-ethoxycarbonyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (3S,4R)-3-hydroxymethyl-4-(isopropylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (13.6 g, 47.4 mmol) in dioxane (200 ml) are added Et_3N (6.64 ml, 47.4 mmol) and 1-[(2-trimethylsilyl)ethoxycarbonyloxy]pyrrolidin-2,5-dione (12.3 g, 47.4 mmol). The mixture is stirred overnight at RT under nitrogen. The solvent is concentrated under reduced pressure and the crude material is taken up in AcOEt, a saturated aqueous solution of $NaHCO_3$ is added and the layers are separated. The aqueous layer is back extracted twice with AcOEt and the combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude residue is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 95:5) to afford the title compound as a yellow oil. TLC, R_f ($MeOH/CH_2Cl_2$ 2:8): 0.65. MS (LC-MS): 417.0 $[M+H]^+$.

C. (3S,4S)-3-Formyl-4-{[isopropyl-(2-trimethylsilanyl-ethoxycarbonyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester

To a well stirred mixture of (3S,4S)-3-hydroxymethyl-4-{[isopropyl-(2-trimethylsilanyl-ethoxycarbonyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester (16.6 g, 39.8 mmol) and Dess-Martin periodinane (16.9 g, 39.8 mmol) in CH_2Cl_2 (110 mL), slowly wet CH_2Cl_2 (0.79 mL of water in 110 mL of CH_2Cl_2) is added. The clear solution becomes cloudy toward the end of wet CH_2Cl_2 addition and is further stirred overnight. Then concentrated to a few mL of solvent by rotary evaporation and taken up in Et_2O. A solution of 1:1 10% $Na_2S_2O_3$ saturated aqueous $NaHCO_3$ is added. The layers are separated and the organic

extract is washed successively with H_2O and brine. The aqueous washings are back-extracted with Et_2O, and this organic layer is washed with H_2O and brine. The combined organic layers are dried with Na_2SO_4, filtered and concentrated. The crude mixture is used in the next step without further purification. TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0.48. MS (LC-MS): 437.0 $[M+Na]^+$.

D. (3R,4S)-3-Cyclopropylaminomethyl-4-{[isopropyl-(2-trimethylsilanyl-ethoxycarbonyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (3S,4S)-3-formyl-4-{[isopropyl-(2-trimethylsilanyl-ethoxycarbonyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester (8.1 g, 19.5 mmol) and cyclopropylamine (1.54 mL, 21.5 mmol) in 1,2-dichloroethane (200 mL) is added $NaBH(OAc)_3$ (6.1 g, 27.3 mmol) and the mixture is stirred overnight. Then diluted with CH_2Cl_2 and washed with an aqueous saturated solution of $NaHCO_3$. The aqueous layer is back extracted twice with CH_2Cl_2 and the combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude material is used in the next step without further purification. TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0.45. MS (LC-MS): 456.2 $[M+H]^+$.

E. (3R,4S)-3-[(Cyclopropyl-phenylacetyl-amino)-methyl]-4-{[isopropyl-(2-trimethylsilanyl-ethoxycarbonyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of phenylacetic acid (1.45 g, 10.53 mmol) and (3R,4S)-3-cyclopropylaminomethyl-4-{[isopropyl-(2-trimethylsilanyl-ethoxycarbonyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester (3.2 g, 7.022 mmol) in CH_2Cl_2 (10 mL), are added triethylamine (1.47 mL, 10.53 mmol) and 1-hydroxy-7-azabenzotriazol hydrate (1.46 g, 10.53 mmol) followed 15 min later by N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide hydrochloride (3.06 g, 15.78 mmol). The resulting mixture is stirred for 2 days at RT, then diluted with CH_2Cl_2 and poured into an aqueous 2M HCl solution. The layers are separated and the aqueous one extracted twice with CH_2Cl_2. The combined organic extracts are neutralized with an aqueous saturated solution of $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated. The crude product is purified by flash chromatography on silica gel (eluent: hexane/AcOEt 2:1). TLC, R_f (hexane/AcOEt 1:1) = 0.42. MS (LC-MS): 574.2 $[M+H]^+$; t_R (HPLC, C18 column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/1.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 6.49 min.

F. (3R,4R)-3-[(Cyclopropyl-phenylacetyl-amino)-methyl]-4-(isopropylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

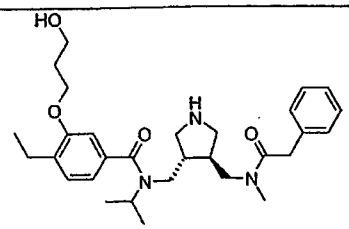
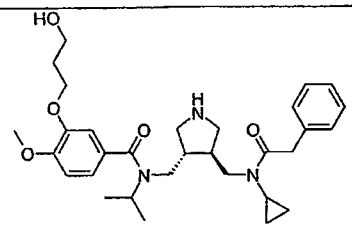
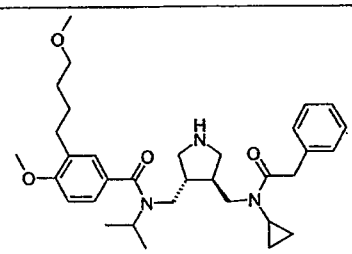
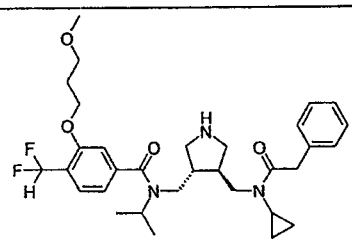
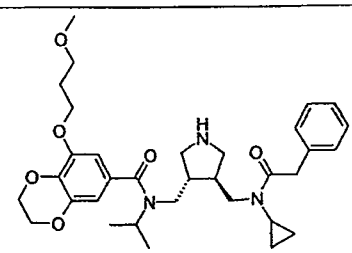
To a solution of (3R,4S)-3-[(cyclopropyl-phenylacetyl-amino)-methyl]-4-{[isopropyl-(2-trimethylsilanyl-ethoxycarbonyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester (2.55 g, 4.44 mmol) in CH_3CN (30 mL) is added tetrabutylammonium fluoride trihydrate (4.34 g, 13.33 mmol) under a nitrogen atmosphere. The reaction mixture is stirred overnight at reflux. The solvent is removed under vacuum and Water and CH_2Cl_2 are added, the layers are separated and the aqueous one extracted twice with CH_2Cl_2. The combined organic extracts are dried (Na_2SO_4), and the solvent is removed *in vacuo*. The crude product is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH/NH_4OH 98:2:1) to give the title product. TLC, R_f (CH_2Cl_2/MeOH/NH_4OH 98:2:1) = 0.11. MS (LC-MS): 430.2 $[M+H]^+$; t_R (HPLC, C18 column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/1.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 3.90 min.

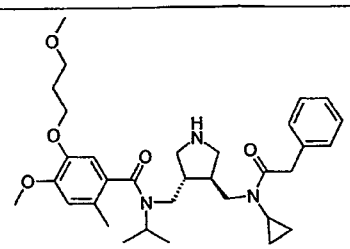
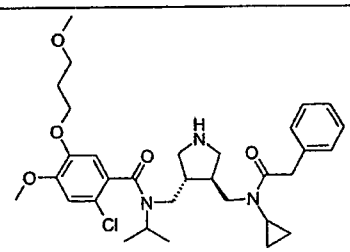
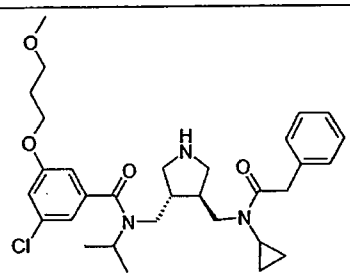
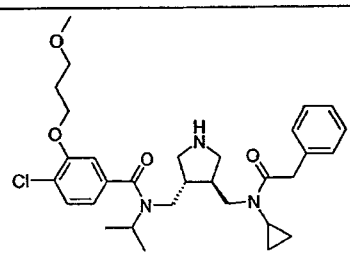
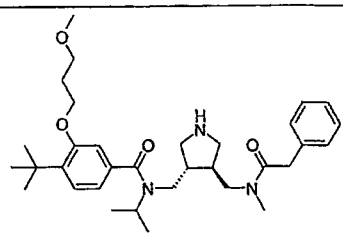
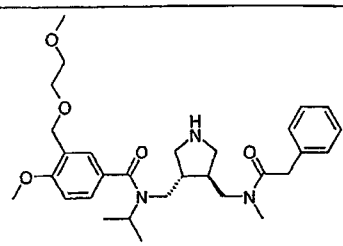
G. (3R,4R)-3-{[(3-Benzyloxy-4-methoxy-benzoyl)-isopropyl-amino]-methyl}-4-[(cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester

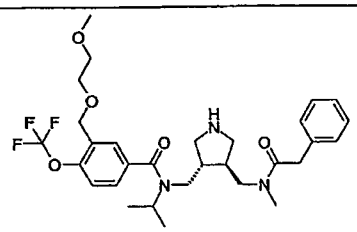
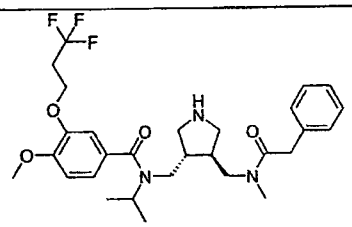
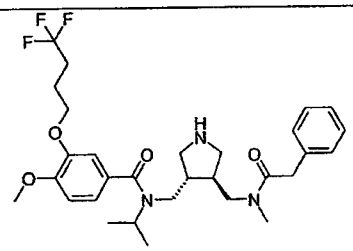
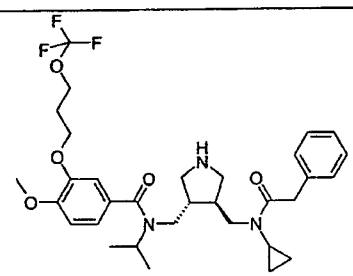
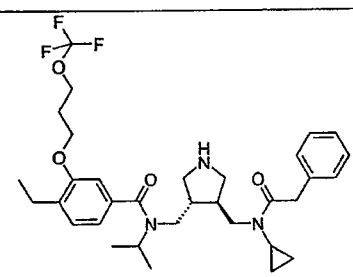
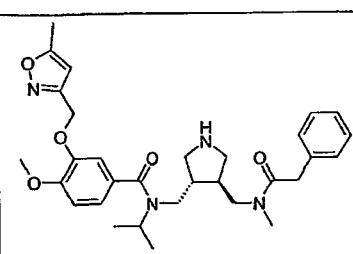
To a solution of 3-benzyloxy-4-methoxy-benzoic acid (0.19 g, 0.734 mmol) and (3R,4R)-3-[(cyclopropyl-phenylacetyl-amino)-methyl]-4-(isopropylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.3 g, 0.489 mmol) in CH_2Cl_2 (10 mL), are added triethylamine (0.102 mL, 0.734 mmol) and 1-hydroxy-7-azabenzotriazol hydrate (0.102 g, 0.734 mmol) followed 15 min later by N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide hydrochloride (0.142 g, 0.734 mmol). The resulting mixture is stirred for 2 days at RT, then diluted with CH_2Cl_2 and poured into an aqueous 2M HCl solution. The layers are separated and the aqueous one extracted twice with CH_2Cl_2. The combined organic extracts are neutralized with an aqueous saturated solution of $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated. The crude product is purified by preparative HPLC. MS (LC-MS): 670.2 $[M+H]^+$; t_R (HPLC, C18 column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/1.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 5.76 min.

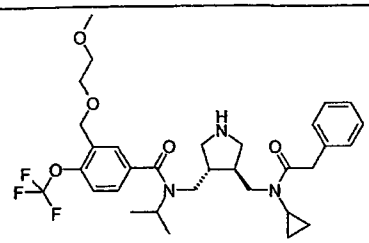
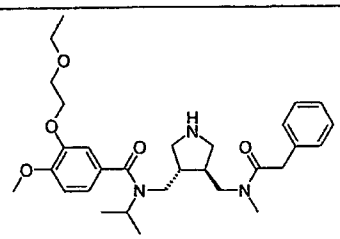
The following Examples are prepared according to the procedures as described above for Example 341, by starting from (3R,4R)-3-[(benzyl-cyclopropyl-amino)-methyl]-4-(isopropylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (or its racemate) and the corresponding substituted benzoic acid.

Table 18:

Example	configuration	structure	$[M+H]^+$	t_R (HPLC)
342	(3S, 4S)		510.4	4.63[a]
343	(3S,4S)		538.2	3.47[c]
344	(3S*, 4S*)		550.2	4.66[c]
345	(3S*, 4S*)		572.2	4.71[c]
346	(3S*, 4S*)		580.2	4.14[c]

347	(3S*, 4S*)		566.2	4.23[c]
348	(3S*, 4S*)		586.2	4.46[c]
349	(3S*, 4S*)		556.2	4.79[c]
350	(3S*, 4S*)		556.2	4.86[c]
351	(3S,4S)		552.4	5.56[b]
352	(3S,4S)		526.2	3.66[c]

353	(3S,4S)		580.2	4.88[b]
354	(3S,4S)		550.2	4.06[c]
355	(3S,4S)		564.2	4.30[c]
356	(3S,4S)		606.2	4.63[c]
357	(3S,4S)		604.2	5.30[b]
358	(3S,4S)		549.2	4.48[b]

359	(3S,4S)		606.2	5.07[a]
360	(3S,4S)		526.2	4.40[a]

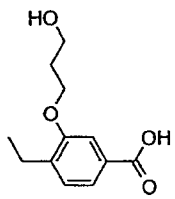
[a] t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min).

[b] t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min).

[c] t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min).

The following intermediates are prepared:

4-Ethyl-3-(3-hydroxy-propoxy)-benzoic acid



a. 4-Ethyl-3-hydroxy-benzoic acid

To a solution of 4-ethyl-3-(3-methoxy-propoxy)-benzoic acid (6.44 g, 27.03 mmol) in CH_2Cl_2 (150 mL) at -78°C is slowly added BBr_3 (9 mL, 93.41 mmol). The reaction mixture is allowed to reach RT and stirred for 3 hours, then poured into ice/water and filtrated to afford the title product as a white solid. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.2.

b. 4-Ethyl-3-hydroxy-benzoic acid methyl ester

To a solution of 4-ethyl-3-hydroxy-benzoic acid (3.76 g, 22.6 mmol) in MeOH (70 mL), cc H_2SO_4 (0.7 mL) is added. The solution is refluxed overnight, then concentrated to about 30 mL and poured into water. The aqueous layer is extracted with ether (50 mL x 4) and the combined organic extracts are neutralized with a saturated aqueous solution of $NaHCO_3$ (50 mL x 2), washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated to give the title compound as a white powder. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.7, MS (LC-MS): 179.2 $[M-H]^-$, t_R (HPLC, Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/2.8 min, flow: 1 ml/min): 4.86 min.

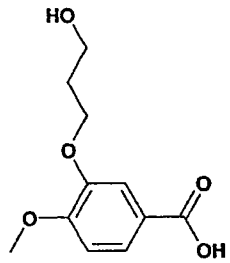
c. 4-Ethyl-3-(3-hydroxy-propoxy)-benzoic acid methyl ester

To a solution of 4-ethyl-3-hydroxy-benzoic acid methyl ester (3.21 g, 17.81 mmol) in acetonitrile (35 mL) are added 3-bromo-1-propanol (1.85 mL, 21.37 mmol) and K_2CO_3 (3.69 g, 26.7 mmol). The solution is refluxed for 4 h, then poured into water and extracted three times with AcOEt. The combined organic extracts are washed with brine, dried over Na_2SO_4, filtered and concentrated to give the title product. TLC, R_f (c-hexane/AcOEt 8:2) = 0.15, MS (LC-MS): 239.2 $[M+H]^+$, t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, flow: 1.5 ml/min): 5.10 min.

d. 4-Ethyl-3-(3-hydroxy-propoxy)-benzoic acid

A solution of 4-ethyl-3-(3-hydroxy-propoxy)-benzoic acid methyl ester (4.68 g, 19.63 mmol) in MeOH (90 mL) and H_2O (5 mL) is treated with NaOH (2.35 g, 58.89 mmol). and heated at reflux for 5 h. The reaction mixture is extracted with AcOEt and the aqueous layer is acidified with HCl 4N and extracted three times with CH_2Cl_2. The combined organic extracts are dried over Na2SO4, filtered and concentrated in vacuo to give the title product. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.1, MS (LC-MS): 223.1 $[M-H]^-$, t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, flow: 1.5 ml/min): 4.47 min.

3-(3-Hydroxy-propoxy)-4-methoxy-benzoic acid



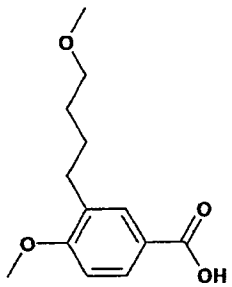
a. 3-(3-Hydroxy-propoxy)-4-methoxy-benzoic acid methyl ester

A mixture of methyl 3-hydroxy-4-methoxybenzoate (4.94 g, 26.6 mmol), 3-bromo-1-propanol (2.86 mL, 31.9 mmol) and anhydrous K_2CO_3 (5.51 g, 39.9 mmol) in MeCN (50 mL) is refluxed with stirring overnight, and after cooling is poured into ice/water. The aqueous layer is extracted with AcOEt, and the combined organics are washed with brine, dried (Na_2SO_4) and concentrated. Purification by flash chromatography on silica gel (hexane/AcOEt 1:2) gives a solid residue which is stirred in a 9:1 mixture of hexane/AcOEt over 30 min. Filtration of the suspension and drying in vacuo gives the title compound as white solid. TLC, R_f (hexane/AcOEt 1:1) = 0.09. MS: 241.2 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 2.86 min. ^{1}H-NMR ($CDCl_3$): δ 2.13 (m, 2H), 2.59 (m, 1H), 3.92 (s, 3H), 3.93 (s, 3H), 4.29 (m, 2H), 6.92 (m, 1H), 7.60 (s, 1H), 7.73 (m, 1H) ppm.

b. 3-(3-Hydroxy-propoxy)-4-methoxy-benzoic acid

A solution of 3-(3-hydroxy-propoxy)-4-methoxy-benzoic acid methyl ester (1.00 g, 4.16 mmol) in THF (3.0 mL) and 2N NaOH (3.1 mL) is stirred at room temperature over 6 hrs. The mixture is adjusted to pH 1 by addition of 2N aqueous HCl to afford a white suspension. The precipitate is filtered, washed with water and dried in vacuo at 50 °C to give the title compound as white solid. MS: 225.0 $[M-H]^+$. ^{1}H-NMR ($CDCl_3$): δ 1.88 (m, 2H), 3.57 (m, 2H), 3.83 (s, 3H), 4.07 (m, 2H), 4.56 (s, br, 1H), 7.06 (dd, 1H), 7.46 (d, 1H), 7.57 (dd, 1H), 12.7 (s, br, 1H) ppm.

4-Methoxy-3-(4-methoxy-butyl)-benzoic acid



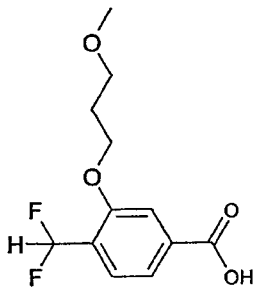
a. 4-Methoxy-3-(4-methoxy-butyl)-benzaldehyde

To a solution of 4-bromo-1-methoxy-2-(4-methoxy-butyl)-benzene (8.10 g, 29.7 mmol; described in EP0678 503 B1) in absolute THF (170 mL), cooled to -78 °C, is added dropwise over 30 min and under an argon atmosphere a 1.6M solution of n-butyllithium in hexane (20.4 mL, 32.6 mmol). After stirring for 5 min, a mixture of DMF (5.03 mL, 65.2 mmol) in THF (20 mL) is added over 30 min at -78 °C. Stirring is continued over 15 min at -78 °C, and the reaction mixture is gradually warmed and stirred for an additional hour at room temperature before quenching with 1N HCl. The aqueous layer is extracted with diethyl ether (3x 200 mL), the combined organics are dried (Na_2SO_4) and concentrated. Purification by flash chromatography on silica gel (hexane/AcOEt 4:1) gives the title compound as yellowish oil. TLC, R_f (hexane/AcOEt 4:1) = 0.27. MS: 223.2 $[M+H]^+$. ^{1}H-NMR ($CDCl_3$): δ 1.6-1.74 (m, 4H), 2.70 (t, 2H), 3.37 (s, 3H), 3.43 (t, 2H), 3.96 (s, 3H), 6.99 (dd, 1H), 7.73 (d, 1H), 7.76 (dd, 1H), 9.70 (s, 1H) ppm.

b. 4-Methoxy-3-(4-methoxy-butyl)-benzoic acid

To a stirred suspension of 4-methoxy-3-(4-methoxy-butyl)-benzaldehyde (300 mg, 1.35 mmol) and sulfamic acid (176 mg, 1.81 mmol) in 80% acetic acid (2.3 mL) is added dropwise a solution of 80% $NaClO_2$ (127 mg, 1.40 mmol; dissolved in 170 µL of H_2O) in water (0.65 mL) over 5 min and by keeping the temperature at 18-20 °C. Stirring of the yellow slurry is continued over 3 hrs at 20 °C before adding another aliquot of 80% $NaClO_2$ (151 mg, 1.67 mmol; dissolved in 205 µL of H_2O), dissolved in water (0.8 mL), and sulfamic acid (130 mg, 1.34 mmol) in 80 % aqueous acetic acid. After stirring overnight, the reaction mixture is diluted by adding water (2.3 mL), the resulting suspension is stirred for 30 min and filtered. The precipitate is dried to give the title product as white solid. TLC, R_f (CH_2Cl_2/MeOH 98:2) = 0.5. MS: 239.0 $[M+H]^+$. ^{1}H-NMR (CD_3OD): δ 1.55-1.7 (m, 4H), 2.65 (t, 2H), 3.31 (s, 3H), 3.41 (t, 2H), 3.89 (s, 3H), 4.87 (s, 1H + D_2O), 6.98 (m, 1H), 7.78 (s, 1H), 7.87 (m, 1H) ppm.

4-Difluoromethyl-3-(3-methoxy-propoxy)-benzoic acid



a. 4-Methyl-benzenesulfinic acid 3-methoxy-propyl ester

Toluene-4-sulfonyl chloride (25.4 g, 133.2 mmol) is slowly added to a solution of 3-methoxy-1-propanol (8.49 mL, 88.8 mmol) and triethylamine (14.8 mL, 106.5 mmol) in CH_2Cl_2 (80 mL) at 0°C. The reaction mixture is then allowed to warm to RT and stirred for another 16 h. The solvent is evaporated, water is added and the mixture is extracted with CH_2Cl_2. Drying (Na_2SO_4) of the combined organic extracts, filtering and evaporation of the solvent affords the crude product which is purified by flash chromatography on silica gel (eluent: c-hexane/AcOEt 5:1) to give the desired product. MS (LC-MS): 262.1 $[M+18]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 5.12 min.

b. 4-Formyl-3-(3-methoxy-propoxy)-benzoic acid 3-methoxy-propyl ester

A mixture of 4-formyl-3-hydroxybenzoic acid (1.5 g, 8.8 mmol), 4-methyl-benzenesulfinic acid 3-methoxy-propyl ester (4.5 g, 18.4 mmol), diisopropylethylamine (3.4 mL, 19.3 mmol) and NaI (2.63 g, 17.5 mmol) in DMF (20 mL) is stirred at 80°C for 60 h and at 130°C for another 5 h. The solvent is partially removed under reduced pressure, water is added and the mixture is extracted with ethyl acetate. Washing (brine) and drying (Na_2SO_4) of the combined organic extracts, filtration and evaporation of the solvent affords the crude product. The desired product is obtained by flash chromatography on silica gel (eluent: c-hexane/AcOEt 3:1). MS (LC-MS): 311.1 $[M+H]^+$; t_R (Zorbax SB C18 column, 10-95% CH_3CN/H_2O/0.8 min, 95% CH_3CN/H_2O, 0.7 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 1.20 min.

c. 4-Difluoromethyl-3-(3-methoxy-propoxy)-benzoic acid 3-methoxy-propyl ester

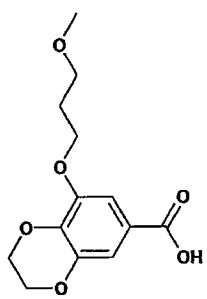
DEOXO-FLUOR (2.8 mL, 15.0 mmol) is slowly added to a solution of 4-formyl-3-(3-methoxy-propoxy)-benzoic acid 3-methoxy-propyl ester (1.81 g, 5.8 mmol) in CH_2Cl_2 (15 mL) at 0°C

under Ar. The reaction mixture is then stirred at RT for 4.5 h, recooled to 0°C before ethanol (7 mL) is added. The mixture is then stirred at RT for another 16 h. The solvent is removed under reduced pressure and the crude product is purified by flash chromatography on silica gel (eluent: c-hexane/AcOEt 3:1) to afford the title compound. MS (LC-MS): 333.1 $[M+H]^+$; t_R (Zorbax SB C18 column, 10-95% CH_3CN/H_2O/0.8 min, 95% CH_3CN/H_2O, 0.7 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 1.26 min

d. 4-Difluoromethyl-3-(3-methoxy-propoxy)-benzoic acid

1N aqueous KOH (6.7 mL, 6.7 mmol) is slowly added to a solution of 4-difluoromethyl-3-(3-methoxy-propoxy)-benzoic acid 3-methoxy-propyl ester (1.48 g, 4.45 mmol) in MeOH (5 mL) and the reaction mixture is stirred at RT for 60 h. For workup the mixture is concentrated under reduced pressure, the residue is taken up in 2N HCl (until a pH = 1 is obtained) and extracted with ethyl acetate. The combined organic extracts are washed with brine, dried (Na_2SO_4), filtered and the solvent is evaporated to give the title compound. MS (LC-MS): 259.1 $[M-H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.89 min

8-(3-Methoxy-propoxy)-2,3-dihydro-benzo[1,4]dioxine-6-carboxylic acid



a. 8-Hydroxy-2,3-dihydro-benzo[1,4]dioxine-6-carboxylic acid ethyl ester

To a solution of 3,4,5-trihydroxy-benzoic acid ethyl ester (5.00 g, 24.2 mmol) in DMF (70 mL) are added 1,2-dibromoethane (2.13 mL, 24.2 mmol) and $CsCO_3$ (16.9 g, 50.9 mmol) and the mixture is stirred overnight at room temperature and for 5 hrs at 60 °C. Extractive work-up with diethyl ether, washing of the organic phase with brine and evaporation gives the crude product as brown oil which is purified by silica gel chromatography (hexane/AcOEt 3:2). The title compound is obtained as a white solid. TLC, R_f (hexane/AcOEt 1:1) = 0.27. MS: 223.0 $[M-H]^+$. ^{1}H-NMR ($CDCl_3$): δ 1.40 (t, 3H), 4.3-4.42 (m, 6H), 5.45 (s, 1H), 7.23 (s, 1H), 7.29 (s, 1H) ppm.

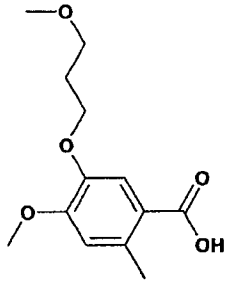
b. 8-(3-Methoxy-propoxy)-2,3-dihydro-benzo[1,4]dioxine-6-carboxylic acid ethyl ester

The mixture of 8-hydroxy-2,3-dihydro-benzo[1,4]dioxine-6-carboxylic acid ethyl ester (1.65 g, 7.36 mmol), 1-bromo-3-methoxypropane (1.38 g, 8.83 mmol) and anhydrous K_2CO_3 (1.53 g, 11.0 mmol) in acetone (40 mL) is refluxed overnight. After cooling to room temperature, the mixture is poured into ice water and extracted with AcOEt. The organic layer is washed with brine, dried (Na_2SO_4) and concentrated. Purification by flash chromatography on silica gel (hexane/AcOEt 3:1) yields the title compound as white solid. TLC, R_f (hexane/AcOEt 1:1) = 0.32. MS: 297.0 $[M+H]^+$. ^{1}H-NMR ($CDCl_3$): δ 1.41 (t, 3H), 2.16 (m, 2H), 3.40 (s, 3H), 3.61 (m, 2H), 4.20 (m, 2H), 4.31 (m, 2H), 4.35-4.45 (m, 4H), 7.27 (d, 1H), 7.31 (d, 1H) ppm.

c. 8-(3-Methoxy-propoxy)-2,3-dihydro-benzo[1,4]dioxine-6-carboxylic acid

The mixture of 8-hydroxy-2,3-dihydro-benzo[1,4]dioxine-6-carboxylic acid ethyl ester (1.85 g, 6.24 mmol) in dioxane (10 mL) and 2N NaOH (5.0 mL) is stirred at 60 °C over 1 h, then cooled to room temperature and acidified (pH 1) with 2N HCl. Volatiles are removed under reduced pressure to afford a suspension. The precipitate is filtered, washed with ice-water and dried in vacuo overnight to give the title product as white solid. TLC, R_f (hexane/AcOEt 2:1 + 1% AcOH) = 0.07. MS: 267.0 $[M-H]^+$. ^{1}H-NMR (DMSO-d_6): δ 1.96 (m, 2H), 3.26 (s, 3H), 3.48 (m, 2H), 4.05 (m, 2H), 4.27 (m, 2H), 4.31 (m, 2H), 7.07 (d, 1H9, 7.11 (d, 1H), 12.8 (s, br, 1H) ppm.

4-Methoxy-5-(3-methoxy-propoxy)-2-methyl-benzoic acid



a. 2-Methoxy-1-(3-methoxy-propoxy)-4-methyl-benzene

A stirred solution of 2-methoxy-4-methylphenol (5.00 g, 36.2 mmol), 1-bromo-3-methoxypropane (7.06 g, 45.2 mmol) and anhydrous K_2CO_3 (7.50 g, 64.3 mmol) is refluxed overnight. After cooling, volatiles are removed under reduced pressure, the residue is taken up in water and extracted with AcOEt. The combined organics are washed with brine, dried

(Na_2SO_4) and concentrated. After silica gel chromatography (hexane/AcOEt 3:1) the title compound is obtained as colorless liquid. TLC, R_f (hexane/AcOEt 2:1) = 0.34. MS: 211.0 $[M+H]^+$. ^{1}H-NMR ($CDCl_3$): δ 2.13 (m, 2H), 2.33 (s, 3H), 3.38 (s, 3H), 3.61 (m, 2H), 3.88 (s, 3H), 4.12 (m, 2H), 6.7-6.85 (m, 3H) ppm.

b. 1-Bromo-4-methoxy-5-(3-methoxy-propoxy)-2-methyl-benzene

To a solution of 2-methoxy-1-(3-methoxy-propoxy)-4-methyl-benzene (2.00 g, 9.51 mmol) in MeCN (30 mL) is added N-bromosuccinimide (1.96 g, 10.5 mmol) at room temperature. Stirring is continued for 2 hrs, followed by evaporation of the solvent. The title compound is obtained after flash chromatography on silica gel (hexane/AcOEt 6:1) as an oil. MS: 289.0/291.0 $[M]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 5.04 min. ^{1}H-NMR ($CDCl_3$): δ 2.13 (m, 2H), 2.36 (s, 3H), 3.39 (s, 3H), 3.58 (m, 2H), 3.87 (s, 3H), 4.12 (m, 2H), 6.77 (s, 1H), 7.08 (s, 1H) ppm.

c. 4-Methoxy-5-(3-methoxy-propoxy)-2-methyl-benzaldehyde

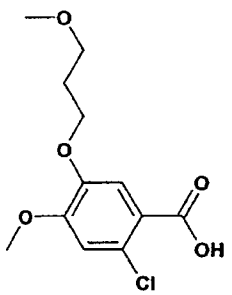
To a solution of 1-bromo-4-methoxy-5-(3-methoxy-propoxy)-2-methyl-benzene (2.50 g, 8.65 mmol) in THF (25 mL), cooled to -70 °C, is added a 1.6M solution of n-buthyllithium in hexane (5.94 mL, 9.51 mmol). After 30 min, DMF (1.05 mL, 13.0 mmol) is added and stirring is continued overnight while the reaction mixture is gradually warmed to room temperature. Quenching with ice-cold 1N aqueous HCl is followed by extraction with diethyl ether. The combined organic layers are washed with brine, dried (Na_2SO_4) and concentrated. Purification by flash chromatography on silica gel (hexane/AcOEt 7:2) gives the title compound as oil. TLC, R_f (hexane/AcOEt 1:1) = 0.29. MS: 239.2 $[M+H]^+$. ^{1}H-NMR ($CDCl_3$): δ 2.16 (m, 2H), 2.66 (s, 3H), 3.39 (s, 3H), 3.60 (m, 2H), 3.97 (s, 3H), 4.18 (m, 2H), 6.73 (s, 1H), 7.40 (s, 1H), 10.2 (s, 1H) ppm.

d. 4-Methoxy-5-(3-methoxy-propoxy)-2-methyl-benzoic acid

To a solution of 4-methoxy-5-(3-methoxy-propoxy)-2-methyl-benzaldehyde (1.25 g, 5.25 mmol) in a 3:1 mixture of tert-butanol/CH_2Cl_2 (60 mL) is added 2-methyl-2-butene (25.0 mL), followed by dropwise addition of a solution of $NaClO_2$ (5.81 g, 51.4 mmol) and NaH_2PO_4 (4.07 g, 33.6 mmol) in water (45 mL) over 15 min at room temperature, and stirring is continued overnight. The reaction mixture is poured into ice/saturated aqueous $NaHCO_3$ solution, the water phase is washed with AcOEt, then acidified and extracted with AcOEt.

The combined organics are washed with brine, dried (Na_2SO_4) and concentrated to give a yellow solid. The crude product is stirred for 30 min in a 95:5 mixture of hexane/diisopropyl ether (25 mL), the precipitate is filtered off, washed with a 95:5 mixture of hexane/diisopropyl ether and dried to give the title compound as yellowish solid. MS: 253.0 $[M-H]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 3.23 min. ^{1}H-NMR ($CDCl_3$): δ 1.96 (m, 2H), 2.51 (s, 3H), 3.27 (s, 3H), 3.48 (m, 2H), 3.84 (s, 3H), 4.00 (m, 2H), 6.89 (s, 1H), 7.41 (s, 1H) ppm.

2-Chloro-4-methoxy-5-(3-methoxy-propoxy)-benzoic acid



a. 2-Chloro-5-hydroxy-4-methoxy-benzaldehyde

2-Chloro-4,5-dimethoxybenzaldehyde (5.00 g, 24.9 mmol; commercially available from Akos Consulting) is dissolved at room temperature in conc. H_2SO_4 (23 mL; Riedel) at room temperature. The deeply colored mixture is heated at 65 °C overnight with stirring, and after cooling is poured with caution into ice-water containing 38 g of solid NaOH (pH 14). The water phase is washed twice with AcOEt, and then is adjusted to pH 1 by addition of HCl 37% with ice-cooling to form a white suspension. Extraction with AcOEt, drying of the organics over $MgSO_4$ and evaporation gives the crude product in a mixture with unreacted starting material. The title compound is obtained after silica gel chromatography (hexane/AcOEt gradient from 3:1 to 1:1) as white solid. TLC, R_f (hexane/AcOEt 1:1) = 0.35. MS: 187.0 $[M+H]^+$. $]^+$. ^{1}H-NMR (DMSO-d_6): δ 3.41 (s, 3H), 7.14 (s, 1H), 7.45 (s, 1H), 9.83 (s, 1H), 10.2 (s, 1H) ppm.

b. 2-Chloro-4-methoxy-5-(3-methoxy-propoxy)-benzaldehyde

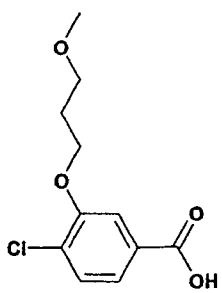
A mixture of crude 2-chloro-5-hydroxy-4-methoxy-benzaldehyde (1.79 g, 8.15 mmol), 1-bromo-3-methoxypropane (1.53 g, 9.79 mmol) and anhydrous K_2CO_3 (1.69 g, 12.2 mmol) in MeCN (30 mL) is refluxed overnight. Ice water is added to the mixture, followed by extraction with AcOEt. The combined organics are washed with brine, dried (Na_2SO_4) and

concentrated. The title compound is obtained after purification by RP-HPLC on a PrepC_{18} OBD column (dimensions: 30x100 mm; 5 µM particle size, SunFire Ltd), and using a 95-5% gradient of MeCN/H_2O 5:95 (containing 0.1% TFA) to MeCN/H_2O 95:5 (containing 0.1% TFA) over 20 min, as white solid. TLC, R_f (hexane/AcOEt 1:1) = 0.42. MS: 259.0 $[M+H]^+$. $]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.15 min. ^{1}H-NMR ($CDCl_3$): δ 2.15 (m, 2H), 3.39 (s, 3H), 3.59 (m, 2H), 3.99 (s, 3H), 4.19 (m, 2H), 6.91 (s, 1H), 7.45 (s, 1H), 10.4 (s, 1H) ppm.

c. 2-Chloro-4-methoxy-5-(3-methoxy-propoxy)-benzoic acid

To a solution of 2-chloro-4-methoxy-5-(3-methoxy-propoxy)-benzaldehyde (1.08 g, 3.55 mmol) in a 3:1 mixture of tert-butanol/CH_2Cl_2 (20 mL) is added 2-methyl-2-butene (0.74 g, 5.32 mmol), followed by dropwise addition of a solution of $NaClO_2$ (0.67g, 7.10 mmol) and NaH_2PO_4 (0.67 g, 4.26 mmol) in water (14 mL) over 15 min at room temperature, and stirring is continued overnight. The reaction mixture is poured into ice/saturated aqueous $NaHCO_3$ solution, the water phase is washed with AcOEt. The ice-cold aqueous layer is acidified with HCl 37% to form a white precipitate which is filtered off, washed with ice-cold water and dried in vacuo. The compound is obtained as white solid. MS: 273.0 $[M-H]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 3.25 min. ^{1}H-NMR ($CDCl_3$): δ 1.96 (m, 2H), 3.25 (s, 3H), 3.47 (m, 2H), 3.85 (s, 3H), 4.03 (m, 2H), 7.10 (s, 1H), 7.39 (s, 1H) ppm.

4-Chloro-3-(3-methoxy-propoxy)-benzoic acid



a. 4-Chloro-3-(3-methoxy-propoxy)-benzoic acid 3-methoxy-propyl ester

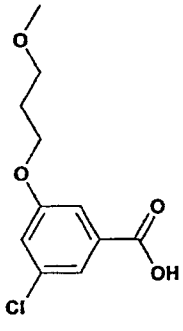
A mixture of 4-chloro-3-hydroxy-benzoic acid (4.02 g, 23.3 mmol; commercially available from Frinton Laboratories), 1-bromo-3-methoxypropane (8.73 g, 55.9 mmol) and anhydrous K_2CO_3 (9.66 g, 69.9 mmol) in MeCN (80 mL) is refluxed overnight. A further amount of 1-

bromo-3-methoxypropane (1.82 g, 0.5 equiv.) is added under reflux conditions. After 2 hrs, the mixture is poured into ice-water and extracted with AcOEt. The combined organics are washed with brine, dried (Na_2SO_4) and concentrated. Flash-chromatography on silica gel (hexane/AcOEt 7:2) affords the title compound as an oil. TLC, R_f (hexane/AcOEt 3:1) = 0.17. MS: 317.2 $[M-H]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 5.13 min. ^{1}H-NMR ($CDCl_3$): δ 2.08 (m, 2H), 2.16 (m, 2H), 3.40 (s, 6H), 3.57 (m, 2H), 3.65 (m, 2H), 4.23 (m, 2H), 4.45 (m, 2H), 7.45 (m, 1H), 7.61 (m, 1H), 7.64 (s, 1H) ppm.

b. 4-Chloro-3-(3-methoxy-propoxy)-benzoic acid

A solution of 4-chloro-3-(3-methoxy-propoxy)-benzoic acid 3-methoxy-propyl ester (1.58 g, 4.99 mmol) in aqueous 2N NaOH (3.23 mL, 6.48mmol) and dioxane (10 mL) is stirred at room temperature for 3.5 hrs. The mixture is acidified by addition of 2N HCl, the volatiles are removed by evaporation and the obtained suspension is filtered. The precipitate is washed with ice-cold water and dried in vacuo to give the title compound as white solid. MS: 243.0 $[M-H]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 3.93 min. ^{1}H-NMR (DMSO-d_6): δ 2.00 (m, 2H), 3.27 (s, 3H), 3.34 (s, br, 1H), 3.53 (m, 2H), 4.19 (m, 2H), 7.5-7.6 (m, 3H) ppm.

3-Chloro-5-(3-methoxy-propoxy)-benzoic acid



a. 3-Chloro-5-(3-methoxy-propoxy)-benzoic acid 3-methoxy-propyl ester

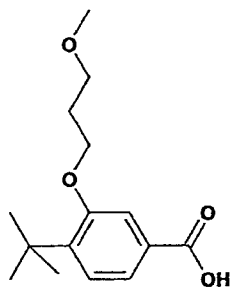
The title compound is obtained from 3-chloro-5-hydroxy-benzoic acid (1.96 g, 11.4 mmol; commercially available from J&W Pharm Lab), 1-bromo-3-methoxypropane (4.25 g, 27.3 mmol) and anhydrous K_2CO_3 (4.71 g, 34.1 mmol), as described above for the 4-chloro regioisomer, as oil. TLC, R_f (hexane/AcOEt 3:1) = 0.21. MS: 317.0 $[M+H]^+$. ^{1}H-NMR ($CDCl_3$):

δ 2.07 (m, 2H), 2.10 (m, 2H), 3.39 (s, 3H), 3.41 (s, 3H), 3.56 (m, 2H), 3.59, (m, 2H), 4.13 (m, 2H), 4.45 (m, 2H), 7.13 (m, 1H), 7.49 (m, 1H), 7.63 (m, 1H) ppm.

b. 3-Chloro-5-(3-methoxy-propoxy)-benzoic acid

The title compound is obtained from 3-chloro-5-(3-methoxy-propoxy)-benzoic acid 3-methoxy-propyl ester (1.70 g, 5.37 mmol), dissolved in dioxane (10 mL), by hydrolysis with 2N aqueous NaOH as a white solid. MS: 243.0 $[M-H]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.04 min. ^{1}H-NMR (DMSO-d_6): δ 1.96 (m, 2H), 3.25 (s, 3H), 3.36 (s, br, 1H), 3.48 (m, 2H), 4.11 (m, 2H), 7.31 (s, 1H), 7.40 (s, 1H), 7.49 (s, 1H) ppm.

4-tert-Butyl-3-(3-methoxy-propoxy)-benzoic acid



a. 4-tert-Butyl-3-methoxy-benzoic acid methyl ester

To a solution of 4-tert-butyl-3-methoxy-benzoic acid (3.00 g, 14.4 mmol; commercially available from Apin, 41226B) in MeOH (30 mL) is added H_2SO_4 conc. (3 mL) and the mixture is refluxed for 5 hrs. After cooling, the mixture is diluted with water, extracted twice with diethyl ether, the combined organics are dried (Na_2SO_4) and evaporated to dryness to give the title compound as yellowish oil. MS: 223.0 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 6.12 min. ^{1}H-NMR ($CDCl_3$): δ 1.41 (s, 9H), 3.91 (s, 3H), 3.92 (s, 3H), 7.36 (dd, 1H), 7.54 (d, 1H), 7.60 (dd, 1H) ppm.

b. 4-tert-Butyl-3-hydroxy-benzoic acid methyl ester

To a solution of borontribromide (3.38 mL, 35.1 mmol) in CH_2Cl_2 (35 mL), cooled to -60 °C, is added under an argon atmosphere a solution of 4-tert-butyl-3-methoxy-benzoic acid methyl ester (2.60 g, 11.7 mmol) in CH_2Cl_2 (65 mL). The reaction is warmed to room temperature and stirring is continued overnight. Another aliquot of BBr_3 (1.13 mL, 11.7

mmol) is added, and the mixture is stirred for 6 hrs at ambient temperature before quenching by careful addition of water. The aqueous layer is extracted with CH_2Cl_2, the combined organics are washed with 1N aqueous NaOH, dried (Na_2SO_4) and concentrated. Purification by flash chromatography on silica gel (eluents: CH_2Cl_2 100%, then CH_2Cl_2/acetone 97:3) gives the title compound as yellowish solid. MS: 209.0 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 5.37 min. ^{1}H-NMR ($CDCl_3$): δ 1.46 (s, 9H), 3.94 (s, 3H), 5.60 (s, 1H), 7.36 (dd, 1H), 7.50 (d, 1H), 7.57 (dd, 1H) ppm.

The alkaline aqueous layers obtained above are acidified with HCl conc., extracted with CH_2Cl_2, the organics are dried (Na_2SO_4) and evaporated to dryness to give 4-tert-butyl-3-hydroxy-benzoic acid: MS: 193.0 $[M+H]^+$. ^{1}H-NMR (DMSO-d_6): δ 1.37 (s, 9H), 7.26 (m, 1H), 7.33 (m, 1H), 7.40 (m, 1H), 9.71 (s, 1H), 12.7 (s, 1H) ppm.

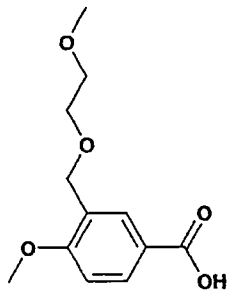
c. 4-tert-Butyl-3-(3-methoxy-propoxy)-benzoic acid methyl ester

A mixture of 4-tert-butyl-3-hydroxy-benzoic acid methyl ester (1.56 g, 7.49 mmol), 3-bromopropyl methyl ether (1.72 g, 11.2 mmol) and anhydrous K_2CO_3 (1.55 g, 11.2 mmol) in MeCN (30 mL) is refluxed overnight. After cooling, the mixture is filtered, the filtrate is diluted with CH_2Cl_2 and the organics are washed with aqueous 0.5M NaOH, aqueous 0.5M HCl and water, dried (Na_2SO_4) and concentrated. Purification by flash chromatography on silica gel (hexane/AcOEt 97:3) gives the title compound as colorless oil. MS: 281.1 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 6.22 min. ^{1}H-NMR ($CDCl_3$): δ 1.43 (s, 9H), 2.17 (m, 2H), 3.41 (s, 3H), 3.65 (m, 2H), 3.93 (s, 3H), 4.18 (m, 2H), 7.36 (dd, 1H), 7.96 (d, 1H), 7.60 (dd, 1H) ppm.

d. 4-tert-Butyl-3-(3-methoxy-propoxy)-benzoic acid

The title compound is obtained by hydrolysis of 4-tert-butyl-3-(3-methoxy-propoxy)-benzoic acid methyl ester (1.60 g, 5.14 mmol), dissolved in EtOH (15 mL), in the presence of aqueous 2N NaOH (3.85 mL, 7.70 mmol) as off-white powder. MS: 284.1 $[M+H_2O]^+$. t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 5.42. ^{1}H-NMR (DMSO-d_6): δ 1.36 (s, 9H), 2.04 (m, 2H), 3.26 (s, 3H), 3.94 (m, 2H), 4.09 (m, 2H), 7.34 (m, 1H), 7.49 (s, 1H), 7.48 (m, 1H), 12.8 (s, br, 1H) ppm.

4-Methoxy-3-(2-methoxy-ethoxymethyl)-benzoic acid



a. (5-Bromo-2-methoxy-phenyl)-methanol

To a suspension of 5-bromo-2-methoxy-benzaldehyde (7.00 g, 32.2 mmol) in MeOH (40 mL), cooled to 0 to 5 °C, is added $NaBH_4$ (1.40 g, 35.4 mmol). After stirring for 1 h, the mixture is poured into ice-water, followed by extraction with AcOEt. The combined organics are washed with brine, dried (Na_2SO_4) and concentrated to give the title product as off-white solid. TLC, R_f (hexane/AcOEt 3:1) = 0.19. ^{1}H-NMR ($CDCl_3$): δ 2.24 (m, 2H), 3.88 (s, 3H), 4.68 (d, 2H), 6.79 (dd, 1H), 7.41 (dd, 1H), 7.45 (d, 1H) ppm.

b. 4-Bromo-1-methoxy-2-(2-methoxy-ethoxymethyl)-benzene

To a solution of (5-bromo-2-methoxy-phenyl)-methanol (3.38 g, 14.8 mmol) and 2-bromoethyl methyl ether (2.06 g, 14.8 mmol) in DMF (30 mL) is added NaH (55% dispersion in oil; 1.36 g, 31.1 mmol) in three portions at room temperature, followed by stirring overnight. The mixture is poured into ice-cooled aqueous 2N HCl, the water phase is extracted with diethyl ether, the combined organic phase is washed with brine, dried (Na_2SO_4) and concentrated. Purification by flash chromatography (hexane/AcOEt 3:1) gives the title compound as liquid. TLC, R_f (hexane/AcOEt 1:1) = 0.44. ^{1}H-NMR ($CDCl_3$): δ 3.45 (s, 3H), 3.64 (m, 2H), 3.71 (m, 2H), 3.83 (s, 3H), 4.60 (s, 2H), 6.76 (d, 1H), 7.37 (dd, 1H), 7.56 (d, 1H) ppm.

c. 4-Methoxy-3-(2-methoxy-ethoxymethyl)-benzoic acid ethyl ester

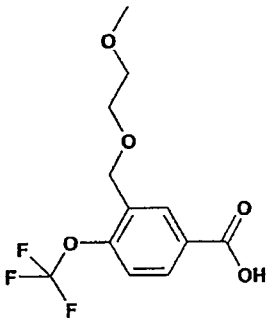
To a solution of 4-bromo-1-methoxy-2-(2-methoxy-ethoxymethyl)-benzene (2.88 g, 10.5 mmol) in absolute THF (30 mL) is added at -70 °C a 1.6N solution of n-butyllithium in hexane (7.20 mL, 11.5 mmol) with stirring. After 40 min, ethyl chloroformate (1.14 g, 10.5 mmol) is added, and the mixture is stirred overnight while gradually warming up to room temperature. The mixture is poured into 2N aqueous HCl, extracted with CH_2Cl_2, the organic layers are dried (Na_2SO_4) and concentrated. The crude product is purified by flash chromatography on

silica gel (hexane/AcOEt 2:1) to give the title compound as liquid. TLC, R_f (hexane/AcOEt 1:1) = 0.13.

d. 4-Methoxy-3-(2-methoxy-ethoxymethyl)-benzoic acid

A solution of 4-methoxy-3-(2-methoxy-ethoxymethyl)-benzoic acid ethyl ester (0.87 g, 3.24 mmol) in a 1:1 mixture of THF and 4N NaOH (10 mL) is stirred at 50 °C overnight. After cooling, the volatiles are removed at reduced pressure, the remaining aqueous phase is acidified to pH 1 by dropwise addition of HCl 37%, and the resulting suspension is filtered off. The precipitate is washed with water, dried overnight in vacuo to give the title compound. TLC, R_f (hexane/AcOEt 1:1) = 0.07. MS: 239.0 $[M-H]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 2.71 min. ^{1}H-NMR (DMSO-d_6): δ 3.29 (s, 3H), 3.52 (m, 2H), 3.64 (m, 2H), 3.88 (s, 3H), 4.51 (s, 2H), 7.10 (m, 1H), 7.90 (m, 1H), 7.94 (m, 1H), 12.6 (s, br, 1H) ppm.

3-(2-Methoxy-ethoxymethyl)-4-trifluoromethoxy-benzoic acid



a. (5-Bromo-2-trifluoromethoxy-phenyl)-methanol

To a solution of 5-bromo-2-trifluoromethoxy-benzoic acid (2.00 g, 7.02 mmol, commercially available from Rare Chemicals, AL BE 0523) and NEt_3 (1.47 mL, 10.5 mmol) in THF (50 mL), cooled to -15 °C and under an argon atmosphere, is added dropwise isobutylchloroformate (1.15 mL, 8.77 mmol). The mixture is stirred for 1 hr after warming to room temperature, followed by addition of AcOEt (20 mL). The organic layer is subsequently washed with 0.5M HCl (20 mL), saturated aqueous $NaHCO_3$ solution (20 mL) and water (20 mL), then dried over Na_2SO_4 and concentrated to give the mixed anhydride intermediate.

To a solution of the mixed anhydride obtained above (1.50 g, 3.90 mmol) in THF (40 mL), cooled to 0-5 °C, is added dropwise a solution of $LiBH_4$ (0.17 g, 7.79 mmol) in THF (5mL). After warming to room temperature, the reaction mixture is stirred overnight and then quenched by adding aqueous 2N NaOH (30 mL). Extraction of the water phase with AcOEt,

drying of the combined organics (Na_2SO_4) and evaporation to dryness gives the title compound as white powder. t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 5.04 min. ^{1}H-NMR (DMSO-d_6): δ 4.56 (d, 2H), 5.51 (t, 1H), 7.31 (dd, 1H), 7.59 (dd, 1H), 7.73 (d, 1H) ppm.

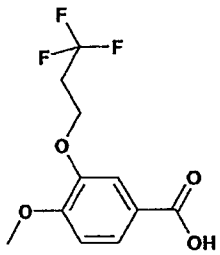
b. 4-Bromo-2-(2-methoxy-ethoxymethyl)-1-trifluoromethoxy-benzene

In a 3-neck flask under argon, a 55-65% dispersion of NaH in oil (0.097 g, 2.44 mmol) is washed with n-pentane, the organics are removed and DMF (10 mL) is added. The mixture is cooled to 0-5 °C, and a solution of (5-bromo-2-trifluoromethoxy-phenyl)-methanol (0.60 g, 2.21 mmol) in DMF (3.0 mL) is added dropwise. After warming to room temperature, stirring is continued for 1 h before this mixture is added to a solution of 2-bromoethyl methyl ether (0.312 mL, 3.32 mmol) in DMF (3mL). After 4 hrs at room temperature, the reaction is still incomplete by TLC. Another aliquot of NaH (1 equiv; oil dispersion washed with pentane) and 2-bromoethyl methyl ether (0.312 mL, 3.32 mmol) are added, followed by stirring for 18 hrs at room temperature. The mixture is poured into ice-water and extracted with AcOEt, the combined organics are dried (Na_2SO_4) and evaporated to dryness to give the title compound as yellowish oil. MS: 346.0/348.0 $[M+H_2O]^+$. t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 5.80 min. ^{1}H-NMR ($CDCl_3$): δ 3.49 (s, 3H), 3.64 (m, 2H), 3.72 (m, 2H), 4.69 (s, 2H), 7.13 (dd, 1H), 7.46 (dd, 1H), 7.77 (d, 1H) ppm.

c. 3-(2-Methoxy-ethoxymethyl)-4-trifluoromethoxy-benzoic acid

To a solution of 4-bromo-2-(2-methoxy-ethoxymethyl)-1-trifluoromethoxy-benzene (0.28 g, 0.85 mmol) in absolute diethyl ether (2.0 mL), cooled to -70 °C, is dropwise added under an argon atmosphere a 1.7M solution of tert.-butyllithium in pentane (0.50 mL, 0.85 mmol). After stirring for 30 min, CO_2 gas is bubbled into the solution for 2 min followed by stirring the yellow solution at -70 °C for additional 30 min. The reaction is quenched by addition of a saturated aqueous NH_4Cl solution (2 mL). The basic aqueous layer is washed with AcOEt and, after acidification to pH 1, is extracted twice with AcOEt. The combined organics are dried over Na_2SO_4 and evaporated to dryness to give the title compound as colorless oil. MS: 293.0 $[M-H]^+$. t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.62 min. ^{1}H-NMR ($CDCl_3$): δ 3.46 (s, 3H), 3.67 (m, 2H), 3.76 (m, 2H), 4.71 (s, 2H), 7.35 (dd, 1H), 8.09 (dd, 1H), 8.35 (dd, 1H) ppm.

4-Methoxy-3-(3,3,3-trifluoro-propoxy)-benzoic acid



a. 4-Methoxy-3-(3,3,3-trifluoro-propoxy)-benzoic acid ethyl ester

The mixture of 3-hydroxy-4-methoxy-benzoic acid ethyl ester (1.75 g, 8.92 mmol), methanesulfonic acid 3,3,3-trifluoro-propyl ester (2.06 g, 10.7 mmol) and anhydrous K_2CO_3 (2.49 g, 17.8 mmol) in acetone (20 mL) is heated with stirring at reflux temperature overnight. After cooling, the mixture is diluted with AcOEt followed by washing of the organic phase with 2N aqueous NaOH and brine. The organic layer is dried over Na_2SO_4 and evaporated, and the crude product is purified by silica gel chromatography (eluent: hexane/AcOEt 5:1) to give the title compound as oil. TLC, R_f (hexane/AcOEt 1:1) = 0.59. MS: 293.0 $[M+H]^+$. ^{1}H-NMR ($CDCl_3$): δ 1.42 (t, 3H), 2.74 (m, 2H), 3.96 (s, 3H), 4.33 (m, 2H), 4.40 (m, 2H), 6.94 (m, 1H), 7.59 (s, 1H), 7.77 (m, 1H) ppm.

b. 4-Methoxy-3-(3,3,3-trifluoro-propoxy)-benzoic acid

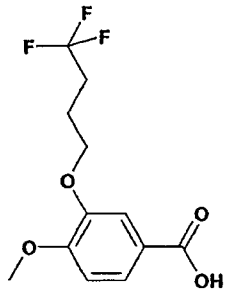
The title compound is obtained as white solid from 4-methoxy-3-(3,3,3-trifluoro-propoxy)-benzoic acid ethyl ester (0.62 g, 2.12 mmol), dissolved in THF (3.0 mL), after hydrolysis in the presence of 2N NaOH (1.6 mL) at 60 °C overnight. The ice-cold reaction mixture is acidified (pH 1) with HCl 37 % to form a white precipitate which is filtered off, washed with water and dried in vacuo. TLC, R_f (hexane/AcOEt 1:1) = 0.17. MS: 263.0 $[M-H]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 3.50 min. ^{1}H-NMR ($CDCl_3$): δ 2..81 (m, 2H), 3.85 (s, 3H), 4.25 (m, 2H), 7.10 (dd, 1H), 7.49 (d, 1H), 7.63 (dd, 1H), 12.6 (s, br, 1H) ppm.

The methanesulfonic acid 3,3,3-trifluoro-propyl ester is prepared according to the following procedure:

To the mixture of 3,3,3-trifluoro-1-propanol (1.28 g, 10.8 mmol) and NEt_3 (4.53 mL, 32.7 mmol) in CH_2Cl_2 (10 mL) is added dropwise at -20 °C methanesulfochloride (1.03 mL, 13.1 mmol). The mixture is slowly warmed over 90 min to 5 °C with stirring, followed by addition of CH_2Cl_2 and washing of the organic layer with 2N aqueous HCl. The organics are dried over

Na_2SO_4 and concentrated in vacuo to give the crude title product as yellowish liquid which was used without further purification. ^{1}H-NMR ($CDCl_3$): δ 2.64 (m, 2H), 3.09 (s, 3H), 4.47 (t, 2H) ppm.

4-Methoxy-3-(4,4,4-trifluoro-butoxy)-benzoic acid



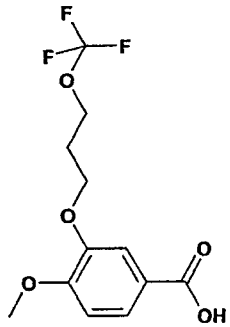
a. 4-Methoxy-3-(4,4,4-trifluoro-butoxy)-benzoic acid ethyl ester

A suspension of 3-hydroxy-4-methoxy-benzoic acid ethyl ester (1.00 g, 5.10 mmol), 1-bromo-4,4,4-trifluorobutane (1.12 g, 5.86 mmol) and anhydrous K_2CO_3 (2.14 g, 15.3 mmol) in MeCN (10 mL) is refluxed with stirring overnight. After cooling, the mixture is filtered, and the filtrates are evaporated to drying to give the title compound as white solid. TLC, R_f (hexane/AcOEt 1:1) = 0.62. MS: 307.0 $[M+H]^+$. ^{1}H-NMR ($CDCl_3$): δ 1.42 (m, 3H), 2.1-2.2 (m, 2H), 2.3-2.45 (m, 2H), 3.95 (s, 3H), 4.14 (m, 2H), 4.39 (m, 2H), 6.93 (dd, 1H), 7.58 (d, 1H), 7.74 (dd, 1H) ppm.

b. 4-Methoxy-3-(4,4,4-trifluoro-butoxy)-benzoic acid

A mixture of 4-methoxy-3-(4,4,4-trifluoro-butoxy)-benzoic acid ethyl ester (0.93 g, 3.04 mmol) in THF (3 mL) and 2N NaOH (2.28 mL, 4.55 mmol) is heated with stirring at 60 °C overnight. After cooling, ice water is added and the pH is adjusted to 1 by addition of HCl 37% to form a white precipitate which is filtered off. The title compound is obtained after drying as white solid. TLC, R_f (hexane/AcOEt 1:1) = 0.17. MS: 277.0 $[M-H]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 3.90 min. ^{1}H-NMR ($CDCl_3$): δ 1.98 (m, 2H), 2.45 (m, 2H), 3.85 (s, 3H), 4.08 (m, 2H), 7.08 (dd, 1H), 7.46 (d, 1H), 7.60 (dd, 1H), 12.7 (s, br, 1H) ppm.

4-Methoxy-3-(3-trifluoromethoxy-propoxy)-benzoic acid



a. Dithiocarbonic acid *O*-(3-ethoxy-propyl) ester *S*-methyl ester

The title compound is prepared by the method described in Bull. Chem. Soc. Jpn. (2000), 73, 477f.: To a cooled solution of 3-ethoxy-1-propanol (24.4 g, 0.227 mol) in DMF (150 mL) is added NaH (60% dispersion in oil; 10.0 g, 0.250 mol) in portions over 1 hour, keeping the reaction temperature below 5 °C. Stirring is continued for 5 hrs at room temperature, the mixture is cooled to 5 to 10 °C followed by dropwise addition of CS_2 (27.5 mL, 0.454 mol). The mixture is gradually warmed to ambient temperature overnight and then cooled to <10 °C before adding iodomethane (17.9 mL, 0.284 mol). Stirring is continued for 18 hrs at room temperature, the mixture is then poured into ice-cold diluted aqueous HCl and extracted with diethyl ether. The combined organic layers are washed with brine, dried over $MgSO_4$ and concentrated to give a yellow oil. Purification by flash chromatography on silica gel (hexane/AcOEt 20:1) gives the title compound as yellow liquid. TLC, R_f (hexane/AcOEt 3:1) = 0.56. ^{1}H-NMR ($CDCl_3$): δ 1.23 (t, 3H), 2.11 (m, 2H), 2.60 (s, 3H), 3.52 (t, 2H), 3.58 (t, 2H), 4.79 (t, 2H) ppm.

b. 1-Ethoxy-3-trifluoromethoxy-propane

Following the method described in Tetrahedron Letters (1992), 33, 4173-4176, a suspension of 1,3-dibromo-5,5-dimethylhydantoin (78.5 g, 0.266 mol) in CH_2Cl_2 (0.8 L) is cooled to -70 °C, followed by dropwise addition of hydrogen fluoride/pyridine (99.2 mL, 3.82 mol; Fluka No 47586). To this mixture is then slowly added a solution of dithiocarbonic acid *O*-(3-ethoxy-propyl) ester *S*-methyl ester (23.0 g, 0.089 mol) in CH_2Cl_2 (200 mL). The yellow reaction mixture is warmed to ambient temperature over 3.5 hrs and then quenched by addition of an ice-cold aqueous solution of $NaHSO_3$/$NaHCO_3$/NaOH until the red-brownish color of the mixture disappears. The aqueous phase is adjusted to pH >10 by addition of solid sodium hydroxide with stirring, the organic phase is separated, washed with brine and filtered. Removal of the solvent (CH_2Cl_2) is achieved by distillation at atmospheric pressure (<35 °C boiling temperature). Fractions boiling between 37 °C and 110 °C are combined, taken up in

CH_2Cl_2 (100 mL) and washed with 2N aqueous HCl. The aqueous layer is re-extracted with CH_2Cl_2 (40 mL), the combined organics are dried (Na_2SO_4) and filtered. The solvent is removed in a distillation apparatus at normal pressure (oil bath at 50 °C) to obtain the title compound as a pale yellow liquid. ^{1}H-NMR ($CDCl_3$): δ 1.23 (t, 3H), 1.98 (m, 2H), 3.48-3.57 (m, 4H), 4.12 (t, 2H) ppm. ^{19}F-NMR ($CDCl_3$): δ -60.8 ppm.

c. Trifluoro-methanesulfonic acid 3-trifluoromethoxy-propyl ester

Following a similar procedure as described in J. Org. Chem. (2001), 66, 1061-1063, 1-ethoxy-3-trifluoromethoxy-propane (1.50 g, 6.10 mmol) is added to a mixture of trifluoromethanesulfonic anhydride (4.04 mL, 23.8 mmol) and trifluoromethanesulfonic acid (0.15 mL, 1.65 mmol) with stirring. The mixture is heated at 60 °C overnight, cooled to room temperature and poured into ice-water. The aqueous layer is extracted with CH_2Cl_2, the combined organics are dried over Na_2SO_4 and filtered. Volatiles are removed by distillation at normal pressure (bath temperature at 65 °C) to give a mixture of trifluoro-methanesulfonic acid ethyl ester and the title compound as pale yellow liquid (used without further purification). ^{1}H-NMR ($CDCl_3$): δ 2.25 (m, 2H), 4.16 (m, 2H), 4.70 (m, 2H) ppm.

d. 4-Bromo-1-methoxy-2-(3-trifluoromethoxy-propoxy)-benzene

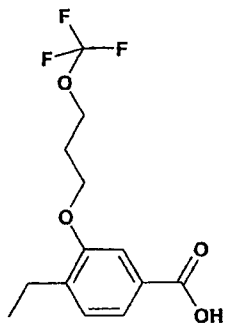
A mixture of 5-bromo-2-methoxy-phenol (1.20 g, 5.62 mmol), crude trifluoro-methanesulfonic acid 3-trifluoromethoxy-propyl ester (2.52 g, 6.74 mmol; purity of 74%) and anhydrous K_2CO_3 (1.18 g, 8.42 mmol) in MeCN (8 mL) is stirred in a sealed flask at room temperature overnight and then filtered. The combined filtrates are concentrated and the crude product is chromatographed over silica gel (eluent: toluene) to give the title compound as oil. TLC, R_f (toluene/AcOEt 10:1) = 0.63. ^{1}H-NMR ($CDCl_3$): δ 2.25 (m, 2H), 3.87 (s, 3H), 4.13 (m, 2H), 4.23 (m, 2H), 6.79 (dd, 1H), 7.04 (d, 1H), 7.09 (dd, 1H) ppm. ^{19}F-NMR ($CDCl_3$): δ -60.7 ppm.

e. 4-Methoxy-3-(3-trifluoromethoxy-propoxy)-benzoic acid

To a solution of 4-bromo-1-methoxy-2-(3-trifluoromethoxy-propoxy)-benzene (1.11 g, 3.20 mmol) in THF (10 mL), cooled to -60 to -70 °C, is added dropwise a 1.6M solution of n-butyllithium in hexane (2.30 mL, 3.69 mmol). After stirring for 30 min, a stream of CO_2 gas is bubbled into the yellow solution for 10 min. The reaction is quenched by adding 2N aqueous HCl and volatiles are removed by evaporation. The water phase is alkalized by addition of 4N NaOH, washed with AcOEt and then acidified with HCl 37% to form a white suspension. Extraction with CH_2Cl_2, drying of the organics over Na_2SO_4 and evaporation gives the title product as white solid. TLC, R_f (hexane/AcOEt 1:1) = 0.09. MS: 293.0 $[M-H]^+$. t_R (HPLC,

Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.00 min. ^{1}H-NMR ($CDCl_3$): δ 2.15 (m, 2H), 3.85 (s, 3H), 4.10 (m, 2H), 4.27 (m, 2H), 7.08 (dd, 1H), 7.48 (d, 1H), 7.60 (dd, 1H) ppm. ^{19}F-NMR (DMSO-d_6): δ -58.2 ppm.

4-Ethyl-3-(3-trifluoromethoxy-propoxy)-benzoic acid



a. 4-Ethyl-3-(3-trifluoromethoxy-propoxy)-benzoic acid methyl ester

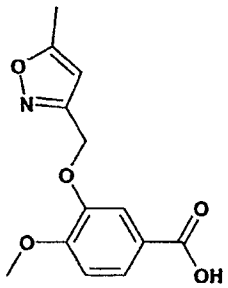
A mixture of 4-ethyl-3-hydroxy-benzoic acid methyl ester (250 mg, 1.32 mmol), crude trifluoro-methanesulfonic acid 3-trifluoromethoxy-propyl ester (590 mg, 1.58 mmol; purity of 74%) and anhydrous K_2CO_3 (276 mg, 1.98 mmol) in MeCN (2.0 mL) is stirred in a sealed glas vial overnight at room temperature. The crude product obtained after filtration and evaporation is purified by flash chromatography (hexane/AcOEt 1:1) to give the title compound as oil. TLC, R_f (hexane/AcOEt 3:1) = 0.38. ^{1}H-NMR ($CDCl_3$): δ 1.24 (t, 3H), 2.25 (m, 2H), 2.70 (q, 2H), 3.94 (s, 3H), 4.18 (t, 2H), 4.24 (t, 2H), 7.25 (d, 1H), 7.52 (s, 1H), 7.64 (d, 1H) ppm. ^{19}F-NMR ($CDCl_3$): δ -61.1 ppm.

b. 4-Ethyl-3-(3-trifluoromethoxy-propoxy)-benzoic acid

The title compound is obtained from 4-ethyl-3-(3-trifluoromethoxy-propoxy)-benzoic acid methyl ester (155 mg, 0.506 mmol) by hydrolysis in THF (3 mL) in the presence of aqueous 2N NaOH (0.38 mL, 0.76 mmol) at 60 °C overnight. After cooling to room temperature, volatiles are removed in vacuo and the residue is portioned between 2N aqueous HCl and CH_2Cl_2. The combined organics are dried (Na_2SO_4) and evaporated to dryness to give the title compound as a white solid. TLC, R_f (hexane/AcOEt 1:1) = 0.17. MS: 291.0 $[M-H]^+$. t_R (HPLC, Nucleosil C18HD column, 20-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.99 min. ^{1}H-NMR (DMSO-d_6): δ 1.15 (t,

3H), 2.18 (m, 2H), 2.64 (q, 2H), 4.13 (t, 2H), 4.29 (t, 2H), 7.28 (d, 1H), 7.45 (s, 1H), 7.51 (d, 1H), 12.65 (s, br, 1H) ppm. ^{19}F-NMR (DMSO-d_6): δ -59.1 ppm.

4-Methoxy-3-(5-methyl-isoxazol-3-ylmethoxy)-benzoic acid



a. 4-Methoxy-3-(5-methyl-isoxazol-3-ylmethoxy)-benzoic acid ethyl ester

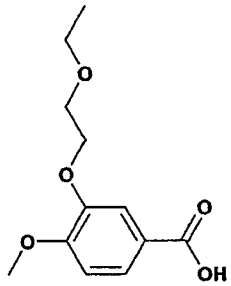
A mixture of 3-hydroxy-4-methoxy-benzoic acid (2.00 g, 10.2 mmol), 3-(chloromethyl)-5-methylisoxazole (1.61 g, 12.2 mmol; commercially available from Maybridge, SPB01262DA), anhydrous K_2CO_3 (2.11 g, 15.3 mmol) and NaI (0.31 g, 2.04 mmol) in MeCN (35 mL) is refluxed overnight. After cooling to room temperature, the mixture is filtered, the filtrate is diluted with CH_2Cl_2 and the organics are washed with aqueous 0.5M NaOH, water and brine. Drying over Na_2SO_4 and evaporation to dryness affords the crude title compound as oil. MS: 292.0 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.14 min. ^{1}H-NMR ($CDCl_3$): δ 1.39 (t, 3H), 2.45 (s, 3H), 3.93 (s, 3H), 4.35 (q, 2H), 5.20 (s, 2H), 6.15 (s, 1H), 6.15 (dd, 1H), 6.90 (d, 1H), 7.70 (dd, 1H) ppm.

b. 4-Methoxy-3-(5-methyl-isoxazol-3-ylmethoxy)-benzoic acid

The title compound is obtained by hydrolysis of 4-methoxy-3-(5-methyl-isoxazol-3-ylmethoxy)-benzoic acid ethyl ester (2.90 g, 8.96 mmol), dissolved in EtOH (25 mL), in the presence of 2N NaOH (6.72 mL, 13.4 mmol) at 70 °C for 3 hrs. After cooling to room temperature, volatiles are removed in vacuo, the aqueous phase is washed with CH_2Cl_2 and then acidified to pH 1 by addition of conc. HCl. The precipitate is filtered off and dried to give an off-white powder. MS: 264.0 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 3.98 min. ^{1}H-NMR (DMSO-d_6): δ 2.39 (s, 3H), 3.82 (s, 3H), 5.15 (s, 2H), 6.30 (s, 1H), 7.06 (dd, 1H), 7.54 (d, 1H), 7.59 (dd, 1H), 12.7 (s, br, 1H) ppm.

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3-(2-Ethoxy-ethoxy)-4-methoxy-benzoic acid



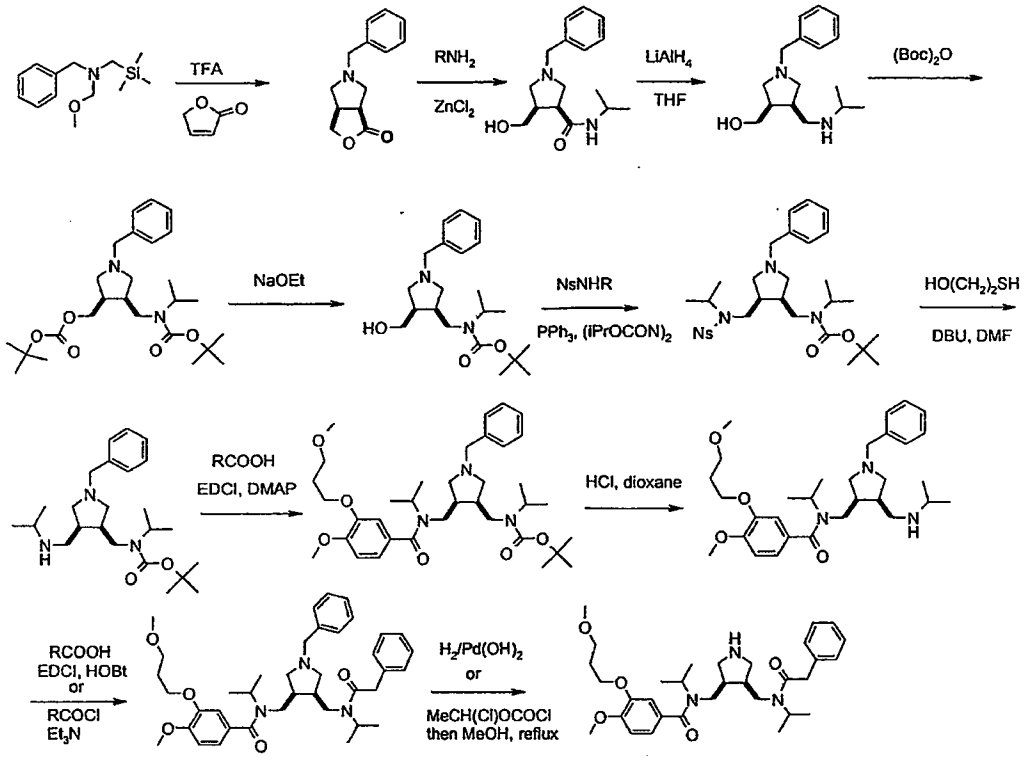
a. 3-(2-Ethoxy-ethoxy)-4-methoxy-benzoic acid ethyl ester

A mixture of 3-hydroxy-4-methoxy-benzoic acid ethyl ester (1.60 g, 8.16 mmol), 2-bromoethyl ethyl ether (1.38 mL, 12.2 mmol) and anhydrous K_2CO_3 (1.69 g, 12.2 mmol) in MeCN (35 mL) is refluxed overnight. In order to complete the reaction, an additional aliquot of 2-bromoethyl ethyl ether (1.38 mL, 12.2 mmol) and a catalytic amount of NaI are added, and reflux is continued overnight. After cooling, the mixture is filtered and the filtrates are concentrated. The residue is taken up in CH_2Cl_2, the organic layer is washed with 0.5M NaOH and water, dried (Na_2SO_4) and concentrated. The title compound is obtained after flash chromatography (hexane/AcOEt 8:2) as colorless oil. MS: 269.0 $[M+H]^+$. t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 4.92 min. ^{1}H-NMR ($CDCl_3$): δ 1.27 (m, 3H), 1.41 (m, 3H), 3.64 (m, 2H), 3.87 (m, 2H), 3.94 (s, 3H), 4.26 (m, 2H), 4.38 (m, 2H), 9.91 (dd, 1H), 7.63 (d, 1H), 7.72 (dd, 1H) ppm.

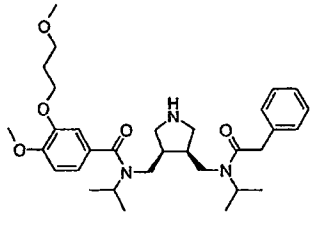
b. 3-(2-Ethoxy-ethoxy)-4-methoxy-benzoic acid

The title compound is obtained from 3-(2-ethoxy-ethoxy)-4-methoxy-benzoic acid ethyl ester (1.41 g, 5.26 mmol) by hydrolysis in EtOH (15 mL) in the presence of aqueous 2N NaOH (3.94 mL, 7.88 mmol) at 50 °C overnight as a white powder. MS: 239.0 $[M-H]^+$. t_R (HPLC, Nucleosil C18HD column, 5-100% CH_3CN/H_2O/6 min, 100% CH_3CN/2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1 mL/min): 3.78 min. ^{1}H-NMR (DMSO-d_6): δ 1.11 (t, 3H), 3.48 (q, 2H), 3.68 (m, 2H), 3.80 (s, 3H), 4.08 (m, 2H), 7.03 (dd, 1H), 7.43 (d, 1H), 7.55 (dd, 1H), 12.6 (s, br, 1H) ppm.

Scheme 7



Example 361: N-Isopropyl-N-{(3R*,4S*)-4-[(isopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-4-methoxy-3-(3-methoxy-propoxy)-benzamide



A solution of N-{(3R*,4S*)-1-benzyl-4-[(isopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide (0.15 g, 0.24 mmol) and 1-chloroethyl chloroformate (0.10 mL, 0.97 mmol) in $ClCH_2CH_2Cl$ is refluxed for 2 h under a nitrogen atmosphere, and MeOH (10 mL) is then added at room temperature. The mixture is heated for 2 h at 80°C, and concentrated to give the title product. For purification, the N-Boc protected compound, (3S*,4R*)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-[(isopropyl-phenylacetyl-amino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester, is prepared analogously as described for the title compound D in Example 361,

Scheme 7. The crude product is purified by flash chromatography on silica gel (eluent: cHexane/AcOEt 50/50) to give the product. MS (LC-MS): 654.4 $[M+H]^+$; t_R (HPLC, C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/2.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 5.92 min.

The pure title compound is prepared analogously as described for the title compound under I in Example 361, Scheme 7. MS (LC-MS): 554.4 $[M+H]^+$; t_R (HPLC, C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 5.23 min.

A. (3aR*,6aS*)-5-Benzyl-hexahydro-furo[3,4-c]pyrrol-1-one

To a mixture of γ-crotonolactone (0.99 mL, 13.5 mmol) and N-(methoxymethyl)-N-(trimethylsilylmethyl)benzylamine (5.0 g, 20.2 mmol) in CH_2Cl_2 (50 mL) is added dropwise TFA (0.10 mL, 1.30 mmol) at 0°C The reaction mixture is stirred overnight at room temperature and quenched with an aqueous saturated solution of $NaHCO_3$ (30 mL). CH_2Cl_2 is added, the layers are separated and the aqueous one back extracted twice with CH_2Cl_2. The combined organic extracts are dried over $MgSO_4$, filtered and concentrated. The crude material is purified by flash chromatography on silica gel (eluent: AcOEt/hexane 10:90 to 20:80) to give the titled product. TLC, Rf (AcOEt/hexane 3:7) = 0.73. MS (LC-MS): 218.1 $[M+H]^+$; t_R (HPLC, C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/2.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 2.95 min.

B. (3S*,4R*)-1-Benzyl-4-hydroxymethyl-pyrrolidine-3-carboxylic acid isopropyl-amide

A suspension of (3aR*,6aS*)-5-benzyl-hexahydro-furo[3,4-c]pyrrol-1-one (1.50 g, 6.90 mmol) and $ZnCl_2$ (0.94 g, 6.90 mmol) in $iPrNH_2$ (20 mL) is refluxed overnight under a nitrogen atmosphere. The crude material is filtered over a pad of Celite and concentrated. The crude material is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH/NH_4OH 70:25:5) to give the title product. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.38. MS (LC-MS): 277.2 $[M+H]^+$.

C. [(3R*,4R*)-1-Benzyl-4-(isopropylamino-methyl)-pyrrolidin-3-yl]-methanol

To a ice-cooled solution of $LiAlH_4$ (0.56 g, 14.76 mmol) in THF (25 mL), is added dropwise a solution of (3S*,4R*)-1-benzyl-4-hydroxymethyl-pyrrolidine-3-carboxylic acid isopropylamide (1.02 g, 3.69 mmol) in THF (5 mL). The reaction mixture is refluxed overnight and quenched with $Na_2SO_4.10\ H_2O$ (4 g) at 0°C. Ether is added, the mixture is stirred for 2 h at room

temperature. The crude material is filtered over a pad of Celite and concentrated to give the title compound which is used without further purification in the next step. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.28. MS (LC-MS): 263.2 $[M+H]^+$; $]^+$; t_R (HPLC, C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/2.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 2.94 min.

D. Carbonic acid (3R*,4S*)-1-benzyl-4-[(tert-butoxycarbonyl-isopropyl-amino)-methyl]-pyrrolidin-3-ylmethyl ester tert-butyl ester

A suspension of [(3R*,4R*)-1-benzyl-4-(isopropylamino-methyl)-pyrrolidin-3-yl]-methanol (1.13 g, 4.31 mmol), $NaHCO_3$ (1.45 g, 17.24 mmol), and Boc_2O (1.88 g, 8.62 mmol) in MeOH (50 mL) is stirred overnignt at room temperature. The mixture is heated for 1 h at 65°C, and then concentrated to a few mL of solvent by rotary evaporation. Water and CH_2Cl_2 are added, the layers are separated and the aqueous one extracted twice with CH_2Cl_2. The combined organic extracts are dried ($MgSO_4$), and concentrated to give the title compound which is used without further purification in the next step. TLC, R_f (AcOEt) = 0.81. MS (LC-MS): 463.3 $[M+H]^+$; t_R (HPLC, C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/2.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 6.08 min.

E. ((3S*,4R*)-1-Benzyl-4-hydroxymethyl-pyrrolidin-3-ylmethyl)-isopropyl-carbamic acid tert-butyl ester

A mixture of carbonic acid (3R*,4S*)-1-benzyl-4-[(tert-butoxycarbonyl-isopropyl-amino)-methyl]-pyrrolidin-3-ylmethyl ester tert-butyl ester (2.02 g, 4.31 mmol) and NaOEt (0.59 g, 8.62 mmol) in EtOH (35 mL) is stirred for 2 h at room temperature. The solvent is concentrated and the residue is diluted by CH_2Cl_2 and H_2O. The layers are separated and the organic extract is washed successively with H_2O and brine. The combined organic layers are dried with $MgSO_4$, filtered and concentrated. The crude material is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 95:5) to give the title product. TLC, R_f (AcOEt) = 0.23. MS (LC-MS): 363.3 $[M+H]^+$; t_R (HPLC, C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/2.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 5.06 min.

F. ((3S*,4R*)-1-Benzyl-4-{[isopropyl-(2-nitro-benzenesulfonyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-isopropyl-carbamic acid tert-butyl ester

To a solution of ((3S*,4R*)-1-benzyl-4-hydroxymethyl-pyrrolidin-3-ylmethyl)-isopropyl-carbamic acid tert-butyl ester (0.60 g, 1.66 mmol), N-isopropyl-2-nitro-benzenesulfon-amide (0.49 g, 1.99 mmol), and PPh_3 (0.52 g, 1.99 mmol) in toluene (15 mL), is added dropwise diisopropyl azodicarboxylate (0.39 mL, 1.99 mmol) at 0°C under a nitrogen atmosphere. The solution is stirred for 1 h at room temperature, and then heated at 65°C for 1 h. The reaction mixture is concentrated. The crude material is used purified by flash chromatography on silica gel (eluent: c-hexane/AcOEt 3:7) to give the crude product. To the solid product is added a mixture of Et_2O/hexane (1:1) and the resulting suspension is filtered. The solid is washed with Et_2O/hexane (1:1) solution, and then the combined filtrate is concentrated to give a titled product. TLC, R_f (AcOEt) = 0.61. MS (LC-MS): 589.3 $[M+H]^+$; t_R (HPLC, C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/2.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 6.39 min.

G. [(3S*,4S*)-1-Benzyl-4-(isopropylamino-methyl)-pyrrolidin-3-ylmethyl]-isopropyl-carbamic acid tert-butyl ester

A solution of ((3S*,4R*)-1-benzyl-4-{[isopropyl-(2-nitro-benzenesulfonyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-isopropyl-carbamic acid tert-butyl ester (8.9 g, 23.02 mmol), 2-mercaptoethanol (0.81 mL, 11.60 mmol), and DBU (0.79 mL, 5.27 mmol) in CH_3CN (10 mL) is stirred for 2 h at room temperature. The mixture is concentrated and then diluted with Et_2O and H_2O. The organic layer is separated, and the aqueous phase is extracted 3 times with Et_2O. The combined organic extracts are dried ($MgSO_4$), and the solvent is concentrated to give the title compound which is used without further purification in the next step. TLC, R_f (AcOEt) = 0.61. MS (LC-MS): 404.3 $[M+H]^+$; t_R (HPLC, C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/2.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.45 min.

H. [(3S*,4R*)-1-Benzyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-isopropyl-carbamic acid tert-butyl ester

To a solution of [(3S*,4S*)-1-benzyl-4-(isopropylamino-methyl)-pyrrolidin-3-ylmethyl]-isopropyl-carbamic acid tert-butyl ester (0.32 g, 0.55 mmol), 4-methoxy-3-(3-methoxy-propoxy)-benzoic acid (0.23 g, 0.96 mmol), DMAP (0.12 g, 0.96 mmol), and triethyl-amine (0.56 mL, 0.96 mmol) in DMF (10 mL), is added EDCI-HCl (0.19 g, 0.96 mmol) at 0°C. The reaction mixture is stirred overnight at room temperature. Water and Et_2O are added, the layers are separated and the aqueous one is extracted twice with Et_2O. The combined

organic extracts are dried ($MgSO_4$), and the solvent is removed *in vacuo*. The crude product is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 90:10) to give the title product. TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0.72. MS (LC-MS): 626.4 $[M+H]^+$; t_R (HPLC, C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/2.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 6.28 min.

I. N-[(3R*,4R*)-1-Benzyl-4-(isopropylamino-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

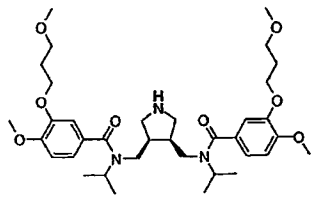
To a solution of [(3S*,4R*)-1-benzyl-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-isopropyl-carbamic acid tert-butyl ester (0.41g, 0.66 mmol), is added a dioxane solution of HCl 4N (10 mL). The reaction mixture is stirred for 2 h at room temperature. The solvent is concentrated and water (20 mL), an aqueous solution of NaOH 4N (5 mL) and Et_2O (25 mL) are added. The layers are separated and the aqueous one extracted twice with Et_2O. The combined organic extracts are dried ($MgSO_4$), and the solvent is removed *in vacuo* to give the title compound which is used without further purification in the next step. MS (LC-MS): 526.4 $[M+H]^+$; t_R (HPLC, C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/2.53 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.78 min.

J. N-{(3R*,4S*)-1-Benzyl-4-[(isopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

To a solution of N-[(3R*,4R*)-1-benzyl-4-(isopropylamino-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide (0.19 g, 0.36 mmol), triethyl-amine (0.15 mL, 1.09 mmol), and DMAP (0.013 g, 0.11 mmol) in CH_2Cl_2, is added dropwise phenyl-acetyl chloride (0.058 mL, 0.44 mmol) at 0°C under a nitrogen atmosphere. The solution is stirred overnight at room temperature. The mixture is added an aqueous solution of NaOH 0.1N (50 mL) and CH_2Cl_2 (50 mL). The organic layer is separated and the aqueous phase extracted twice with CH_2Cl_2, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 90:10) to give the title product. TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0.23. MS (LC-MS): $[M+H]^+$; 644.4 t_R (HPLC, C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/2.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 5.95 min.

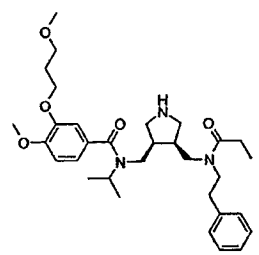
The following Examples are prepared according to the procedures described above for Example 361 :

Example 362: N-Isopropyl-N-{(3R*,4S*)-4-[(isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzoyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-4-methoxy-3-(3-methoxy-propoxy)-benzamide



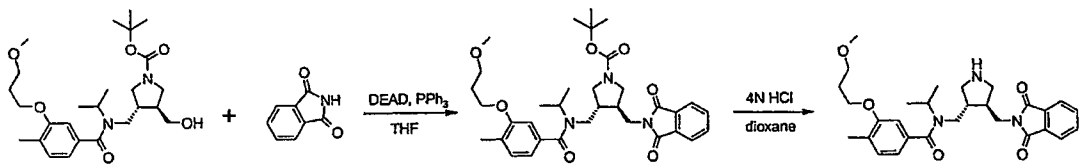
The title compound is prepared analogously as described in Example 361 by coupling N-[(3R*,4R*)-1-benzyl-4-(isopropylamino-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide and 3-(3-methoxy-propoxy)-4-methoxy-benzoic acid in step J. MS (LC-MS): 658.3 $[M+H]^+$; t_R (HPLC, Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/2.5 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 5.20 min.

Example 363: N-Isopropyl-4-methoxy-3-(3-methoxy-propoxy)-N-{(3R,4S)-4-[(phenethyl-propionyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-benzamide

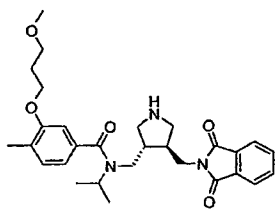


The title compound is prepared analogously as described in Example 361 using ((3S*,4R*)-1-benzyl-4-hydroxymethyl-pyrrolidin-3-ylmethyl)-isopropyl-carbamic acid tert-butyl ester and 2-nitro-N-phenethyl-benzenesulfonamide in step F, then propionyl chloride as the acylating agent in step H and 3-(3-methoxy-propoxy)-4-methoxy-benzoic acid as acylating agent in step J. MS (LC-MS): 554.4 $[M+H]^+$; t_R (HPLC, Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 5.26 min.

Scheme 8



Example 364: N-[(3S,4S)-4-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide



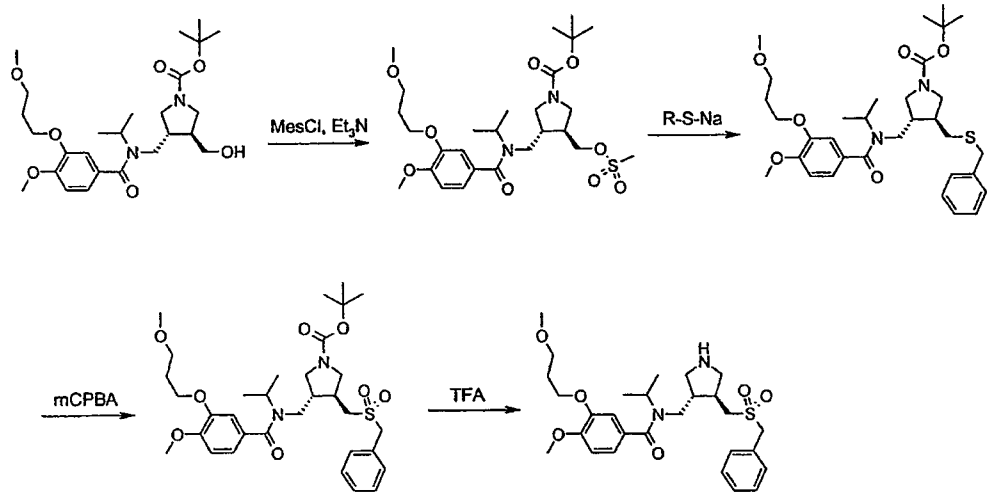
(3R,4R)-3-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (180 mg, 0.30 mmol) is dissolved 4N HCl in dioxane (5 mL) and stirred at RT for 30 min. Lyophilization affords the corresponding hydrochloride salt. MS (LC-MS): 508.1 $[M+H]^+$; t_R (HPLC, Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min): 2.58 min.

The starting material is prepared as follows:

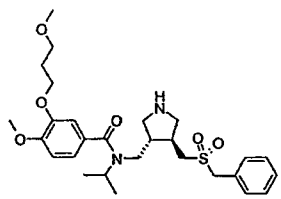
(3R,4R)-3-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

DEAD is slowly added to a solution of (3S,4R)-3-hydroxymethyl-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (210 mg, 0.44 mmol), phthalimide (07 mg, 0.66 mmol) and PPh_3 (173 mg, 0.66 mmol) in THF (5 mL) at RT. The resulting yellow solution is stirred for another 2 h before H_2O is added and the mixture is extracted with ethyl acetate. Drying (Na_2SO_4) of the extracts, filtration and evaporation of the solvent affords the crude product which is purified by preparative HPLC (Waters C_{18} ODB, eluent: CH_3CN/H_2O 5%/2 min, CH_3CN/H_2O 5-100%/10 min, 100% CH_3CN/2.5 min, flow 20 mL/min) to give the desired product. MS (LC-MS): 630.2 $[M+Na]^+$; t_R (HPLC, Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min): 4.40 min.

Scheme 9:

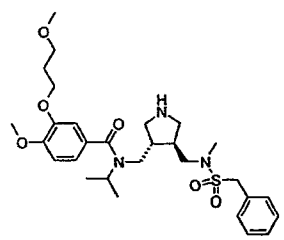


Example 365: N-Isopropyl-4-methoxy-3-(3-methoxy-propoxy)-N-((3S*,4S*)-4-phenyl-methanesulfonyl methyl-pyrrolidin-3-ylmethyl)-benzamide



The title compound is prepared as shown in Scheme 9.

Example 366: N-Isopropyl-4-methoxy-3-(3-methoxy-propoxy)-N-{(3S*,4S*)-4-[(methyl-phenylmethanesulfonyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-benzamide



To a solution of (3R*,4S*)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-[(methyl-phenylmethanesulfonyl-amino)-methyl]-pyrrolidine-1-carboxylic acid tert-

butyl ester (49 mg, 0.074 mmol) in 2 mL CH_2Cl_2, TFA (86 µL, 1.11 mmol) is added. The mixture is stirred 4 h at RT and then poured into a saturated solution of $NaHCO_3$. The layers are separated, and the aqueous one is back-extracted twice with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude material is purified by flash chromatography on an Isolute SPE Flash NH_2 column (eluent: CH_2Cl_2/MeOH 100:0 to 95:5) to give the title product. TLC, R_f (CH_2Cl_2/MeOH 9:1) = 0.2. MS (LC-MS): 563.0 $[M+H]^+$; t_R (HPLC, Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.55 min.

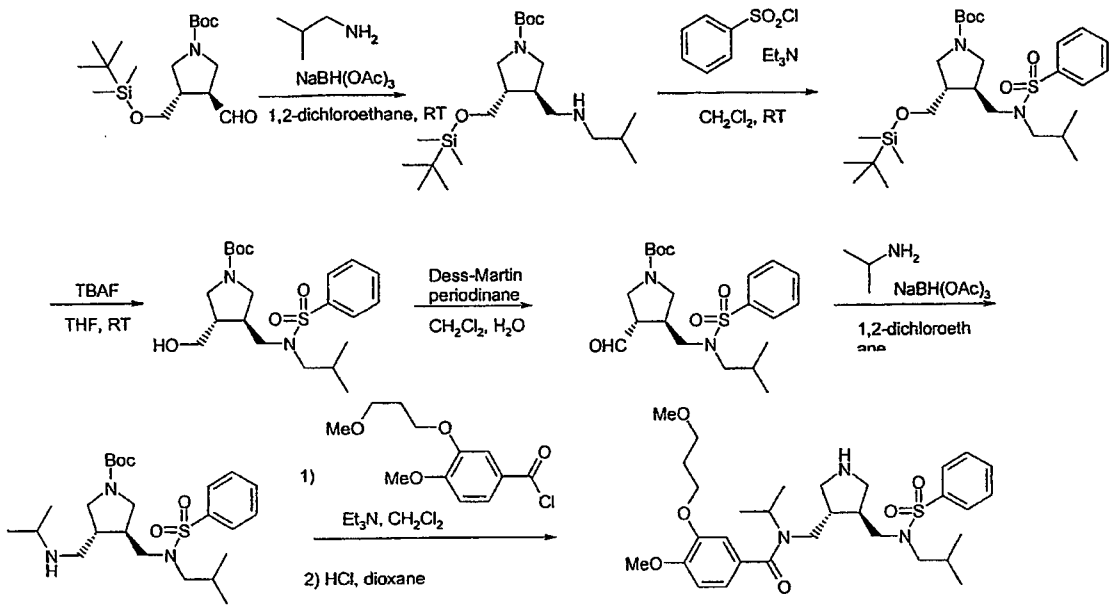
To a solution of the free base in dioxane (2 mL), 4N HCl in dioxane (0.074 mmol, 19 µL) is added, and the resulting solution is lyophilized to afford the corresponding hydrochloride salt as a white powder.

The starting material is prepared as follows:

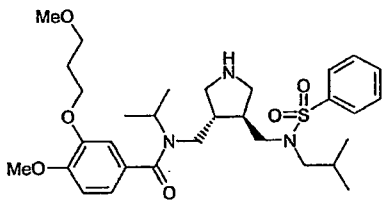
(3R*,4S*)-3-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-[(methyl-phenylmethanesulfonyl-amino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester

To a solution of (3R*,4R*)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-methylaminomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester (89 mg, 0.175 mmol) in CH_2Cl_2 (3 mL), alpha-toluenesulfonyl chloride (40 mg, 0.21 mmol) and triethylamine (30 µL, 0.21 mmol) are added under N_2 atmosphere. The mixture is stirred overnight at RT, diluted with CH_2Cl_2 and poured into an aqueous saturated solution of $NaHCO_3$. The organic layer is separated, and the aqueous one is extracted twice with CH_2Cl_2. The combined organic extracts are dried over Na_2SO_4, filtered and concentrated. The crude product is purified by preparative HPLC (C18-ODB-AQ, 5 µm, 20x50 mm, YMC, eluent: CH_3CN /H_2O + 0.1 % HCOOH flow: 20 mL/min). The HPLC fractions are collected, and the resulting solution is lyophilized to afford the title product. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.3. t_R (HPLC, Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 ml/min): 5.81 min.

Scheme 10



Example 367: N-Isopropyl-4-methoxy-3-(3-methoxy-propoxy)-N-{(3S*,4S*)-4-[(isobutyl-phenylsulfonyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-benzamide



4N HCl/dioxane (4 mL) is added to a solution of (3R*,4R*)-3-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-[(isobutyl-phenylsulfonyl-amino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester (0.804 g, 1.17 mmol) in dioxane (5 mL). After 3 h the solution is lyophilized to give the title compound a a colorless powder. MS (LC-MS): 590.3 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.91 min.

The starting material is prepared as follows:

A. (3S*,4R*)-3-(tert-Butyl-dimethyl-silanyloxymethyl)-4-(isobutylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

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The title compound is prepared as described above for Example 9 / step F (Scheme 5) from (3S*,4S*)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-formyl-pyrrolidine-1-carboxylic acid tert-butyl ester and isobutylamine. MS (LC-MS): 401.1 $[M+H]^+$; t_R (HPLC, Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min): 3.70 min.

B. N-[(3S*,4S*)-4-(tert-Butyl-dimethyl-silanyloxymethyl)-pyrrolidin-3-ylmethyl]-N-isobutyl-benzenesulfonamide

The title compound is prepared as described above in Example 366 / step A from (3S*,4R*)-3-(tert-butyl-dimethyl-silanyloxymethyl)-4-(isobutylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester and phenylsulfonyl chloride. TLC, R_f (CH_2Cl_2/MeOH 98:2) = 0.42; t_R (HPLC, Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min): 5.58 min.

C. N-((3S*,4S*)-4-Hydroxymethyl-pyrrolidin-3-ylmethyl)-N-isobutyl-benzenesulfonamide

The title compound is prepared as described above for Example 9 / step H (Scheme 5) from N-[(3S*,4S*)-4-(tert-butyl-dimethyl-silanyloxymethyl)-pyrrolidin-3-ylmethyl]-N-isobutyl-benzenesulfonamide. MS (LC-MS): 327.1 $[M-Boc+H]^+$; t_R (HPLC, Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min): 4.17 min.

D. N-((3S*,4S*)-4-Formyl-pyrrolidin-3-ylmethyl)-N-isobutyl-benzenesulfonamide

The title compound is prepared as described above for Example 9 / step E (Scheme 5) from N-((3S*,4S*)-4-Hydroxymethyl-pyrrolidin-3-ylmethyl)-N-isobutyl-benzenesulfonamide. MS (LC-MS): 325.0 $[M-Boc+H]^+$; t_R (HPLC, Waters Symmetry C18 column, 20-95% CH_3CN/H_2O/3.5 min, 95% CH_3CN/H_2O, 2 min, CH_3CN and H_2O containing 0.1% TFA, flow: 0.6 mL/min): 4.24 min.

E. (3S*,4R*)-3-[(Benzenesulfonyl-isobutyl-amino)-methyl]-4-(isopropylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound is prepared as described above for Example 9 / step F (Scheme 5) from N-((3S*,4S*)-4-formyl-pyrrolidin-3-ylmethyl)-N-isobutyl-benzenesulfonamide and isopropylamine. MS (LC-MS): 468.1 $[M+H]^+$; t_R (HPLC, Macherey-Nagel Nucleosil C18

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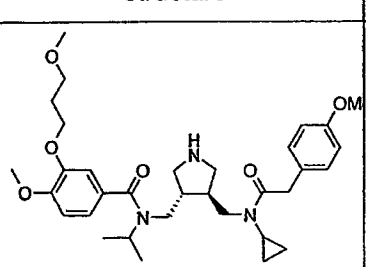
column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 4.94 min.

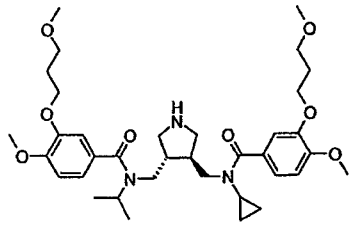
F. (3R*,4R*)-3-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-4-[(isobutyl-phenylsulfonyl-amino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester

Triethylamine (0.48 mL, 3.43 mmol) followed by 3-(3-methoxy-propoxy)-4-methoxy-benzoic acid chloride (621 mg, 2.4 mmol) (prepared from 3-(3-methoxy-propoxy)-4-methoxy-benzoic acid and $SOCl_2$ in CH_2Cl_2) is added to a solution of (3S*,4R*)-3-[(benzenesulfonyl-isobutyl-amino)-methyl]-4-(isopropylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (1.07 g, 2.3 mmol) in CH_2Cl_2 (30 mL) and stirred at RT for 16 h. For workup a sat. solution of $NaHCO_3$ is added and the mixture is extracted with ethyl acetate. The combined organic extracts are dried (Na_2SO_4), filtered and the solvent is evaporated. Purification of the crude product by flash chromatography on silica gel (eluent gradient: c-hexane/AcOEt1:1 to 3:7) yields the title compound. TLC, R_f (c-hexane/AcOEt 3:7) = 0.40; t_R (HPLC, Macherey-Nagel Nucleosil C18 column, 10-100% CH_3CN/H_2O/5 min, 100% CH_3CN/3 min, CH_3CN and H_2O containing 0.1% TFA, flow: 1.5 mL/min): 6.10 min.

The following Examples are prepared according to the procedures described above in Examples 8, 9, 10, 11, 12 and 13:

Table 19:

Example	configuration	structure	$[M+H]^+$	t_R (HPLC)
368	(3S*, 4S*)		582.4	4.51

369	(3S,4S)		656.4	4.37

Conditions RP-HPLC: column: Nucleosil C18-HD (4 x 70 mm, 3 µM); solvent A: H_2O/0.1% TFA, solvent B: MeCN/0.1% TFA; gradient: 5-100% solvent B over 6 min, then 100% solvent B over 1.5 min, then 100 to 5% solvent B over 0.5 min; flow: 1.0 mL/min.

Example 370: Soft Capsules

5000 soft gelatin capsules, each comprising as active ingredient 0.05 g of any one of the compounds of formula I mentioned in any one of the preceding Examples, are prepared as follows:

1. Composition

Active ingredient	250 g
Lauroglycol	2 liters

Preparation process: The pulverized active ingredient is suspended in Lauroglykol® (propylene glycol laurate, Gattefossé S.A., Saint Priest, France) and ground in a wet pulverizer to produce a particle size of about 1 to 3 µm. 0.419 g portions of the mixture are then introduced into soft gelatin capsules using a capsule-filling machine.

Example 371: Tablets comprising compounds of the formula I

Tablets, comprising, as active ingredient, 100 mg of any one of the compounds of formula I in any one of the preceding Examples are prepared with the following composition, following standard procedures:

Composition

Active Ingredient	100 mg
crystalline lactose	240 mg
Avicel	80 mg
PVPPXL	20 mg
Aerosil	2 mg

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magnesium stearate	5 mg
	447 mg

Manufacture: The active ingredient is mixed with the carrier materials and compressed by means of a tabletting machine (Korsch EKO, stamp diameter 10 mm).

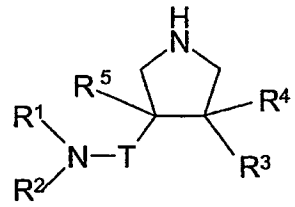
Avicel® is microcrystalline cellulose (FMC, Philadelphia, USA). PVPPXL is polyvinyl-polypyrrolidone, cross-linked (BASF, Germany). Aerosil® is silicon dioxide (Degussa, Germany).

Example 372: Renin inhibiting activity of the compounds in examples 1 to 369:

Using the test systems mentioned above, IC_{50} values for the compounds in the preceding examples 1 to 369 can be found in the range from 1 nM to 20 μM.

What is claimed is:

1. The use of a compound of the formula I,



(I)

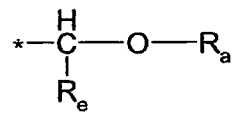
wherein

R^1 is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, unsubstituted or substituted alkenyl, substituted or unsubstituted alkynyl or acyl;

R^2 is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, unsubstituted or substituted alkenyl, substituted or unsubstituted alkynyl or acyl;

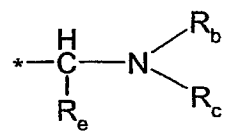
R^3 is a moiety selected from the group of moieties of the formulae

(a)

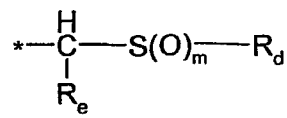


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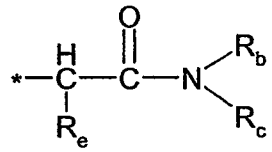
(b)



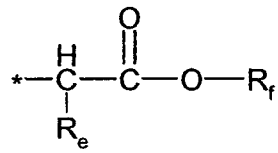
(c)



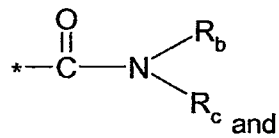
(d)



(e)

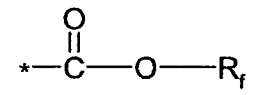


(f)



and

(g)



,

where in any of the moieties of the formulae given above under (a), (b), (c), (d), (e), (f) and (g) the asterisk (*) shows the bond binding the respective moiety R^3 to the rest of the molecule in formula I,

R_a is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, acyl or hydrogen;

R_b and R_c are independently selected from the moieties given under R_a, with the proviso that preferably not more than one of R_b and R_c is acyl, or R_b and R_c may form together a 3 to 7 membered nitrogen containing ring which can be unsubstituted or substituted;

Rd is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or acyl, or can have one of these meanings or can be $-N(R_b)(R_c)$ if m is 1 or preferably 2;

R_e is hydrogen, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or substituted or preferably unsubstituted C_1-C_7-alkyl; and
R_f is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl;
m is 0, 1 or 2;
each of R^4 and R^5 is selected, independently from the other, from hydrogen, unsubstituted or substituted alkyl, hydroxy or esterified or etherified hydroxy;
and T is methylene, methylene mono-substituted by alkyl, or is carbonyl or thiocarbonyl;
or a pharmaceutically acceptable salt thereof,
in the preparation of a pharmaceutical formulation for the treatment of a disease that depends on activity of renin.

2. The use according to claim 1 of a compound of the formula I wherein

R^1 is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, unsubstituted or substituted alkenyl, substituted or unsubstituted alkynyl or acyl;
R^2 is unsubstituted or substituted mono- or bicyclic aryl-alkyl;
R^3 is a moiety selected from the group of moieties of the formulae (a), (b), (c), (d), (e), (f) or (g) given in the first description of a compound of the formula I in this disclosure;
where in any of the moieties of these moiety formulae the asterisk (*) shows the bond binding the respective moiety R^3 to the rest of the molecule in formula I,
R_a is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, acyl or hydrogen;

R_b and R_c are independently selected from the moieties given under R_a, with the proviso that preferably not more than one of R_b and R_c is acyl,

Rd is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or (preferably if m is 0) acyl, or can have one of these meanings or can be $-N(R_b)(R_c)$ if m is 1 or preferably 2;

R_e is unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or substituted or preferably unsubstituted C_1-C_7-alkyl or hydrogen; and

R_f is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl;

m is 0, 1 or 2;

each of R^4 and R^5 is selected, independently from the other, from hydrogen, unsubstituted or substituted alkyl, hydroxy or esterified or etherified hydroxy, preferably hydrogen;

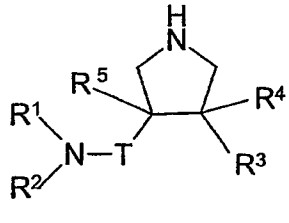
and T is methylene ($-CH_2-$), methylene mono-substituted by alkyl (-[C(H)(alkyl)]-) , carbonyl (-C(=O)-) or thiocarbonyl (-C(=S)-);

or a pharmaceutically acceptable salt thereof,

in the preparation of a pharmaceutical formulation for the treatment of a disease that depends on activity of renin.

3. The use according to claim 1 or according to claim 2 where the disease to be treated is hypertension.

4. A compound of the formula I,



(I)

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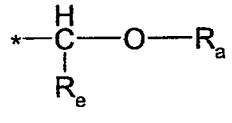
wherein

R^1 is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, unsubstituted or substituted alkenyl, substituted or unsubstituted alkynyl or acyl;

R^2 is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, substituted monocyclic or unsubstituted or substituted bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, unsubstituted or substituted alkenyl, substituted or unsubstituted alkynyl; with the proviso that if R^1 is one of the moieties mentioned in the definition of R^1 other than acyl then R^2 can also be unsubstituted monocyclic aryl-alkyl;

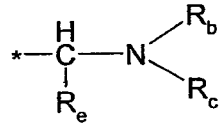
R^3 is a moiety selected from the group of moieties of the formulae

(a)

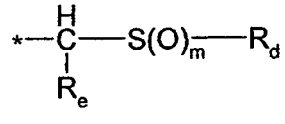


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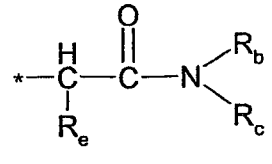
(b)



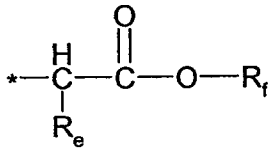
(c)



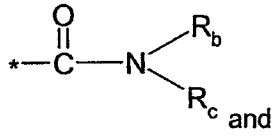
(d)



(e)

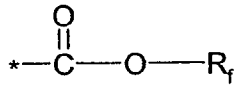


(f)



and

(g)



where in any of the moieties of the formulae given above under (a), (b), (c), (d), (e), (f) and (g) the asterisk (*) shows the bond binding the respective moiety R^3 to the rest of the molecule in formula I,

R_a is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, acyl or hydrogen;

R_b and R_c are independently selected from the group consisting of unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, acyl or hydrogen, with the proviso that preferably not more than one of R_b and R_c is acyl, and with the proviso that if R_c is one of the mentioned moieties other than acyl then R_b can also be unsubstituted or substituted monocyclic aryl-alkyl; or R_b and R_c may form together a 3 to 7 membered nitrogen containing ring which can be unsubstituted or substituted;

Rd is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or acyl, or can have one of these meanings or can be $-N(R_b)(R_c)$ if m is 1 or preferably 2;

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R_e is hydrogen, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or substituted or preferably unsubstituted C_1-C_7-alkyl; and

R_f is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl;

m is 0, 1 or 2;

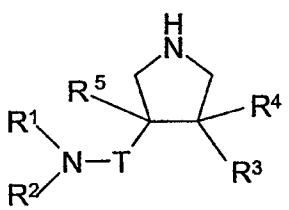
each of R^4 and R^5 is selected, independently from the other, from hydrogen, unsubstituted or substituted alkyl, hydroxy or esterified or etherified hydroxy;

and T is methylene, methylene mono-substituted by alkyl, or is carbonyl or thiocarbonyl;

or a pharmaceutically acceptable salt thereof,

for use in the treatment of a mammal.

5. A compound of the formula I,



(I)

wherein

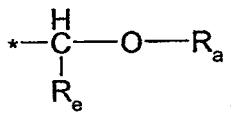
R^1 is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, unsubstituted or substituted alkenyl, substituted or unsubstituted alkynyl or acyl;

R^2 is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, unsubstituted or substituted alkenyl, substituted or unsubstituted alkynyl;

with the proviso that if R^1 is one of the moieties mentioned in the definition of R^1 other than acyl then R^2 can also be unsubstituted or substituted monocyclic aryl-alkyl;

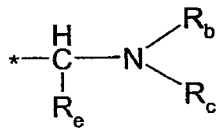
R^3 is a moiety selected from the group of moieties of the formulae

(a)

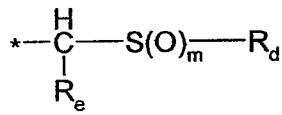


;

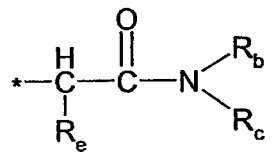
(b)



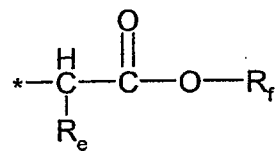
(c)



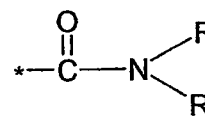
(d)



(e)

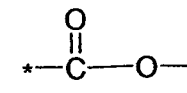


(f)



and

(g)



,

where in any of the moieties of the formulae given above under (a), (b), (c), (d), (e), (f) and (g) the asterisk (*) shows the bond binding the respective moiety R^3 to the rest of the molecule in formula I,

R_a is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, acyl or hydrogen;

R_b and R_c are independently selected from the group consisting of unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl, acyl or hydrogen, with the proviso that preferably not more than one of R_b and R_c is acyl, and with the proviso that if R_c is one of the mentioned moieties other than acyl then R_b can also be unsubstituted or substituted monocyclic aryl-alkyl; or R_b and R_c may form together a 3 to 7 membered nitrogen containing ring which can be unsubstituted or substituted;

Rd in a moiety of the formula (c) is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or acyl, or can have one of these meanings or can be $-N(R_b)(R_c)$ if m is 1 or preferably 2;

R_e is hydrogen, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or substituted or preferably unsubstituted C_1-C_7-alkyl; and

R_f is substituted alkyl or preferably unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl;

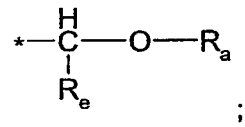
m is 0, 1 or 2;

each of R^4 and R^5 is selected, independently from the other, from hydrogen, unsubstituted or substituted alkyl, hydroxy or esterified or etherified hydroxy;

and T is methylene, methylene mono-substituted by alkyl, carbonyl or thiocarbonyl;
or a salt thereof.

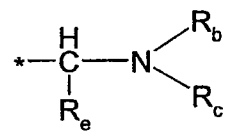
6. A compound of the formula I according to claim 5
wherein
R^1 is acyl;
R^2 is unsubstituted or substituted cycloalkyl or preferably unsubstituted or substituted alkyl,
R^3 is a moiety selected from the group of moieties of the formulae

(a)

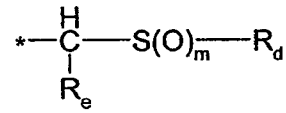


;

(b)

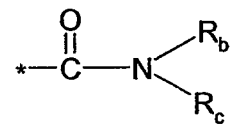


(c)



and

(f)



and

where in any of the moieties of the formulae given above under (a), (b), (c) and (f) the asterisk (*) shows the bond binding the respective moiety R^3 to the rest of the molecule in formula I,
R_a is acyl or hydrogen;
R_b is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl or acyl;
R_c is hydroxy-C_1-C_7-alkyl, C_1-C_7-alkyloxy-C_1-C_7-alkyl or preferably C_3-C_8-cycloalkyl, hydrogen or C_1-C_7-alkyl;
R_d is unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl;
R_e is hydrogen (preferred) or C_1-C_7-alkyl; and

3/5

m is 2;

each of R^4 and R^5 is selected, independently from the other, from hydrogen, unsubstituted or substituted alkyl, hydroxy or esterified or etherified hydroxy;
and T is methylene, methylene mono-substituted by alkyl, carbonyl or thiocarbonyl;
or an (especially pharmaceutically acceptable) salt thereof.

7. The use according to any one of claims 1 to 3, the compound of the formula I or a pharmaceutically acceptable salt thereof for use according to claim 4 or the compound of formula I or a salt thereof according to any one of claims 5 or 6, wherein one or more, preferably all of the substituent and symbol definitions where mentioned are as follows:

"C_1-C_7-" defines a moiety with up to and including maximally 7, especially up to and including maximally 4, carbon atoms, said moiety being branched one or more times or straight-chained and bound via a terminal or a non-terminal carbon, for example, C_1-C_7-alkyl is n-pentyl, n-hexyl or n-heptyl or preferably C_1-C_4-alkyl, especially methyl, ethyl, n-propyl, sec-propyl, n-butyl, isobutyl, sec-butyl, tert-butyl;

halo or halogen is fluoro, chloro, bromo or iodo, most preferably fluoro, chloro or bromo;

unsubstituted or substituted mono- or bicyclic aryl is a mono- or bicyclic aryl with 6 to 22 carbon atoms, whereby one of the rings of the bicyclic aryl may be a partially or fully saturated ring condensed to the other aromatic ring, especially phenyl, indanyl, indenyl, 1,2,3,4-tetrahydronaphthyl or naphthyl, and is unsubstituted or substituted by one or more, especially one to three, moieties, preferably independently selected from the group consisting of

a substituent of the formula -(C_0-C_7-alkylene)-$(X)_r$-(C_1-C_7-alkylene)-$(Y)_s$-(C_0-C_7-alkylene)-H (especially in substituted aryl or substituted aryl-alkyl as R^1) where C_0-alkylene means that a bond is present instead of bound alkylene, alkylene in each case may be straight-chained or branched and unsubstituted or (with lower preference) substituted e.g. by one or more moieties as defined for substituted alkyl, especially by halo, especially fluoro, hydroxy, C_1-C_7-alkoxy, phenyloxy, naphthyloxy, C_1-C_7-alkanoyloxy, benzoyloxy, naphthoyloxy, amino, mono- or di-(C_1-C_7-alkyl, C_1-C_7-alkanoyl, phenyl-C_1-C_7-alkanoyl, naphthyl-C_1-C_7-alkanoyl, phenyl,

naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-amino, carboxy, C_1-C_7-alkoxycarbonyl or cyano, r and s, each independently of the other, are 0 or 1 and each of X and Y, if present and independently of the others, is -O-, -NV-, -S-, -O-CO-, -CO-O-, -NV-CO-; -CO-NV-; -NV-SO_2-, -SO_2-NV; -NV-CO-NV-, -NV-CO-O-, -O-CO-NV-, -NV-SO_2-NV- wherein V is hydrogen or unsubstituted or substituted alkyl as defined below, especially C_1-C_7-alkyl, or is phenyl, naphthyl, phenyl- or naphthyl-C_1-C_7-alkyl or halo-C_1-C_7-alkyl; e.g. the substituent of said formula is C_1-C_7-alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl or tert-butyl, halo-C_1-C_7-alkyl, such as trifluoromethyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, such as 3-methoxypropyl or 2-methoxyethyl, C_1-C_7-alkoxy-C_1-C_7-alkoxy-C_1-C_7-alkyl, phenyloxy- or naphthyloxy-C_1-C_7-alkyl, C_1-C_7-alkanoyloxy-C_1-C_7-alkyl, amino-C_1-C_7-alkyl, such as aminomethyl, C_1-C_7-alkoxy-C_1-C_7-alkylamino-C_1-C_7-alkyl, mono- or di- (C_1-C_7-alkyl-, naphthyl-, phenyl, naphthyl-C_1-C_7-alkyl and/or phenyl-C_1-C_7-alkyl)-amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino-C_1-C_7-alkyl, C_1-C_7-alkyl-O-CO-NH-C_1-C_7-alkyl, C_1-C_7-alkylsulfonylamino-C_1-C_7-alkyl, C_1-C_7-alkyl-NH-CO-NH-C_1-C_7-alkyl, C_1-C_7-alkyl-NH-SO_2-NH-C_1-C_7-alkyl, C_1-C_7-alkoxy, hydroxy-C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7alkoxy, C_1-C_7-alkanoyloxy, halo-C_1-C_7-alkoxy, such as trifluoromethoxy, phenyl- or naphthyl-C_1-C_7-alkanoyloxy, phenyl- or naphthyl-C_1-C_7-alkylaminocarbonyloxy, halo-C_1-C_7-alkylthio, such as trifluoromethylthio, phenyl- or naphthyl-C_1-C_7-alkylthio, mono- or di-(C_1-C_7-alkyl-, naphthyl-C_1-C_7-alkyl-, phenyl-C_1-C_7-alkyl- and/or C_1-C_7-alkoxy-C_1-C_7-alkyl-)amino, C_1-C_7-alkanoylamino, C_1-C_7-alkylsulfonylamino, phenyl- or naphthyl-C_1-C_7-alkanoylamino, phenyl- or naphthyl-C_1-C_7-alkylaminocarbonylamino, carboxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-carbonyl, hydroxy-C_1-C_7-alkoxycarbonyl, C_1-C_7-alkoxy-C_1-C_7-alkoxycarbonyl, amino-C_1-C_7-alkoxy-carbonyl, (N-) mono-(C_1-C_7-alkyl)-amino-C_1-C_7-alkoxycarbonyl, C_1-C_7-alkanoylamino-C_1-C_7-alkoxycarbonyl, N- mono- or N,N-di-(C_1-C_7-alkyl, naphthyl-C_1-C_7.alkyl and/ or phenyl-C_1-C_7-alkyl)-aminocarbonyl, C_1-C_7-alkylsulfonyl, halo-C_1-C_7-alkylsulfonyl, hydroxy-C_1-C_7-alkylsulfonyl, C_1-C_7-alkoxy-C_1-C_7-alkylsulfonyl, amino-C_1-C_7-alkylsulfonyl, N-mono- or di-(C_1-C_7-alkyl)-amino-C_1-C_7-alkylsulfonyl, C_1-C_7-alkanoylamino-C_1-C_7-alkylsulfonyl, N-C_1-C_7-alkoxy-C_1-C_7-alkylcarbamoyl or N-mono- or N,N-di-(C_1-C_7-alkyl)-aminosulfonyl;

from C_2-C_7-alkenyl, C_2-C_7-alkynyl, phenyl, naphtyl, mono- or bicyclic heterocyclyl, especially as defined below for mono- or bicyclic heterocyclyl, preferably selected from pyrrolyl, furanyl, thienyl, pyrimidine-2,4-dione-1-, -3- or –5-yl and tetrahydrofuranyl, , phenyl- or naphthyl- or (mono- or bicyclic heterocyclyl)-C_1-C_7-alkyl or C_1-C_7-alkyloxy wherein mono- or bicyclic heterocyclyl is as defined below, preferably selected from pyrrolyl, furanyl, tetrahydrofuranyl, tetrahydropyranyl and thienyl ; such as benzyl or naphthylmethyl, tetrahydrofuranyl- or

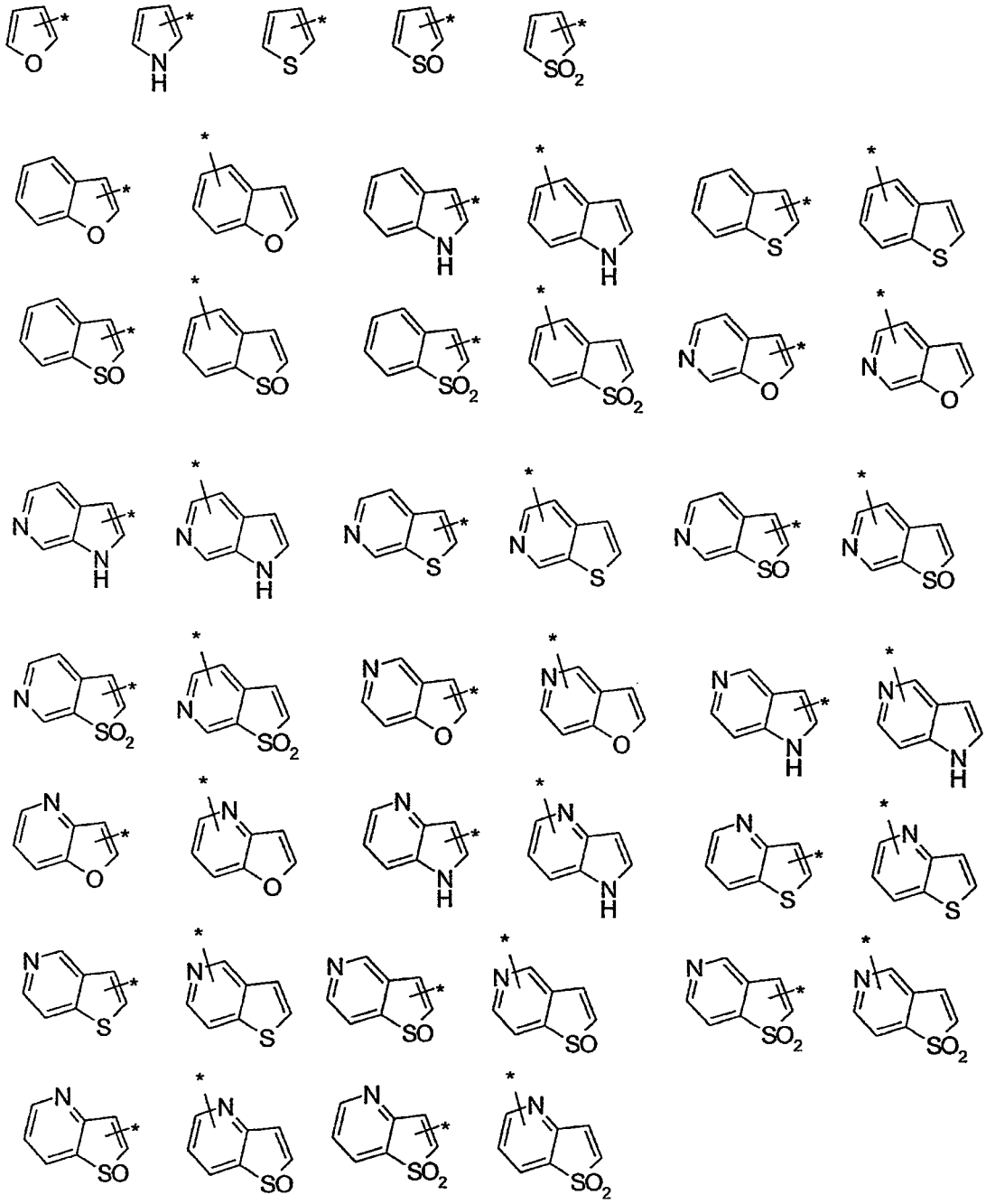
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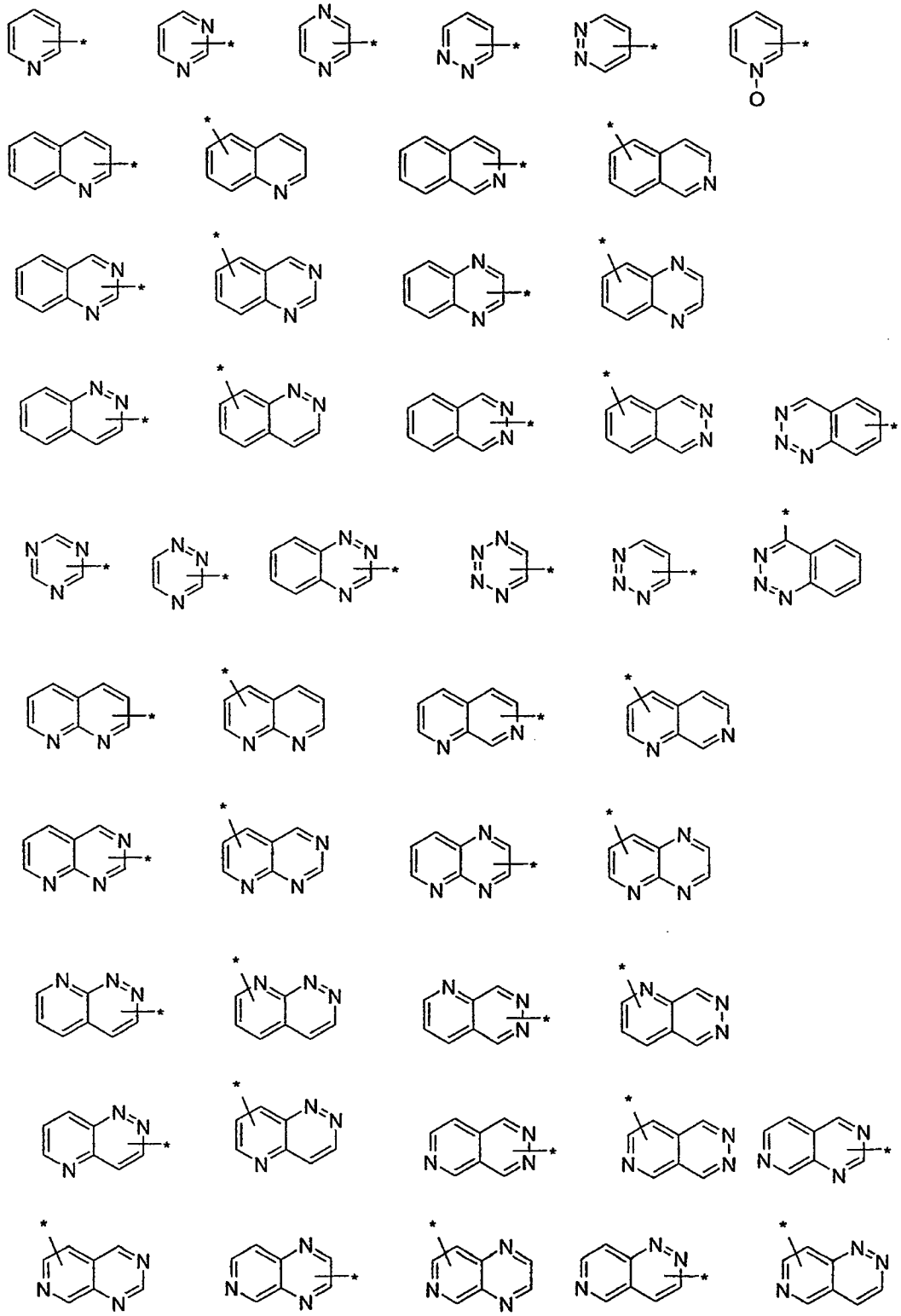
tetrahydropyranyl-C_1-C_7-alkyloxycarbonyl, benzoyl- or naphthoylamino-C_1-C_7-alkyl, (phenyl- or naphthyl- or mono- or bicyclic heterocyclyl)-sulfonylamino-C_1-C_7-alkyl (wherein phenyl or naphthyl or mono- or bicyclic heterocyclyl is unsubstituted or substituted, preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkylsulfonylamino-C_1-C_7-alkyl, halo, hydroxy, phenyl-C_1-C_7-alkoxy wherein phenyl is preferably unsubstituted or substituted, preferably by C_1-C_7-alkoxy and/or halo, mono- or bicyclic heterocyclyl-C_1-C_7-alkoxy, (mono- or bicyclic heterocyclyl or phenyl or naphthyl)-oxy, naphthyl-C_1-C_7-alkyloxy, benzoyl, naphthoyl or mono- or bicyclic heterocyclylcarbonyl)-oxy, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-aminocarbonyloxy, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-thio, (benzoyl or naphthoyl or mono- or bicyclic heterocyclyl)-thio, nitro, amino, di-((naphthyl or phenyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkyl)-amino, (benzoyl or naphthoyl or mono- or bicyclic heterocyclyl)-amino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-sulfonylamino wherein phenyl or naphthyl is unsubstituted or substituted preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkylsulfonylamino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-aminocarbonylamino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-oxycarbonylamino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkyloxycarbonylamino, carboxyl, C_1-C_7-alkyl-carbonyl, halo-C_1-C_7-alkylcarbonyl, hydroxy-C_1-C_7-alkylcarbonyl, C_1-C_7-alkoxy-C_1-C_7-alkylcarbonyl, amino-C_1-C_7-alkylcarbonyl, (N-) mono- or (N,N-) di-(C_1-C_7-alkyl)-amino-C_1-C_7-alkylcarbonyl, C_1-C_7-alkanoylamino-C_1-C_7-alkylcarbonyl, halo-C_1-C_7-alkoxycarbonyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-oxy-carbonyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkoxycarbonyl, (N,N-) di-(C_1-C_7-alkyl)-amino-C_1-C_7-alkoxycarbonyl, carbamoyl, N-mono or N,N-di-(naphthyl or phenyl or mono- or bicyclic heterocyclyl)-aminocarbonyl, cyano, C_1-C_7-alkylene which is unsubstituted or substituted by up to four C_1-C_7-alkyl substituents and bound to two adjacent ring atoms of the aryl moiety, sulfenyl, sulfinyl, C_1-C_7-alkylsulfinyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-sulfinyl wherein phenyl or naphthyl is unsubstituted or substituted preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, phenyl- or naphthyl-C_1-C_7-alkylsulfinyl, sulfonyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-sulfonyl wherein phenyl or naphthyl is unsubstituted or substituted preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkylsulfonyl, sulfamoyl and N-mono or N,N-di-(C_1-C_7-alkyl,

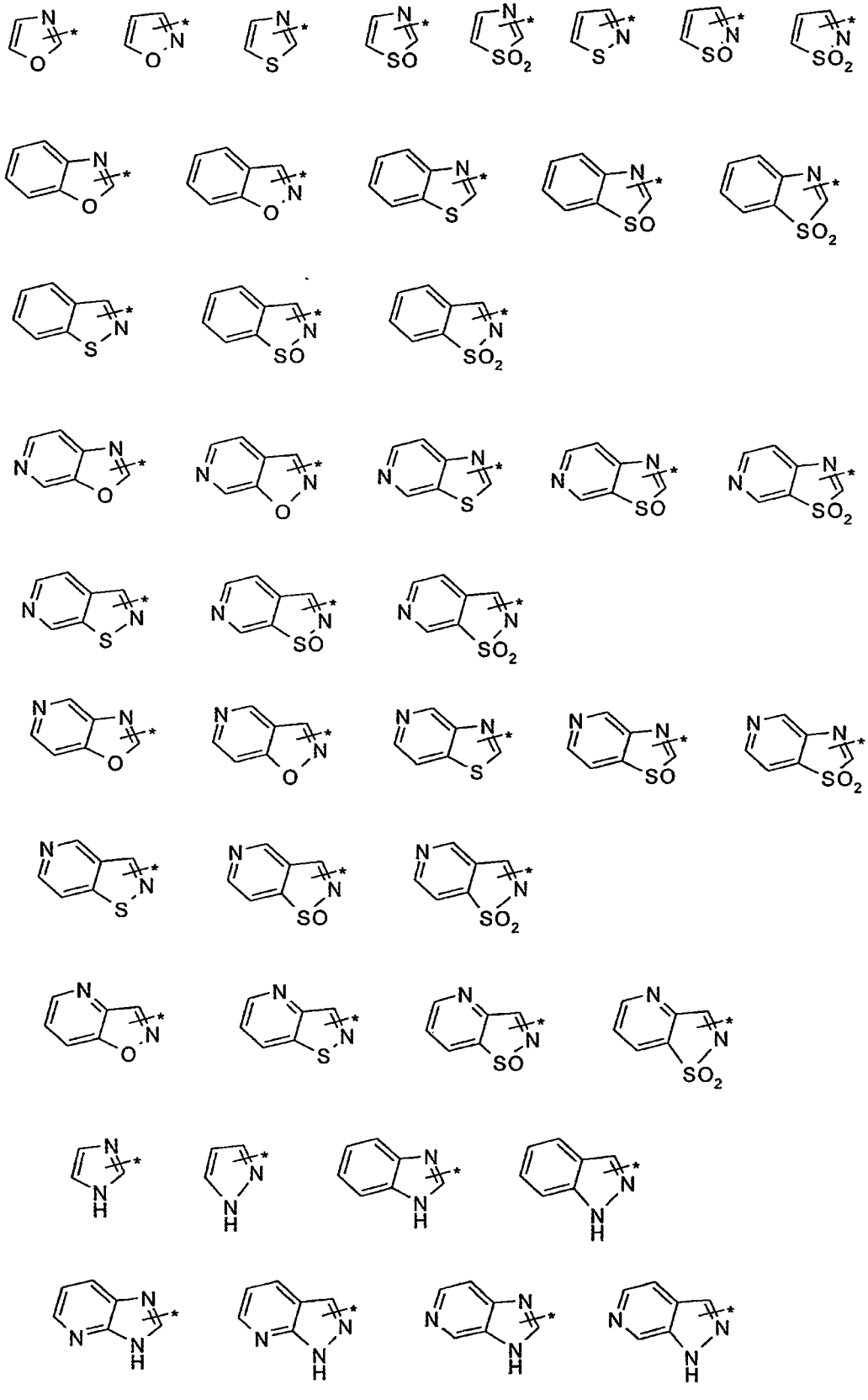
phenyl-, naphthyl, mono- or bicyclic heterocyclyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl and/or mono- or bicyclic heterocyclyl-C_1-C_7-alkyl)-aminosulfonyl;

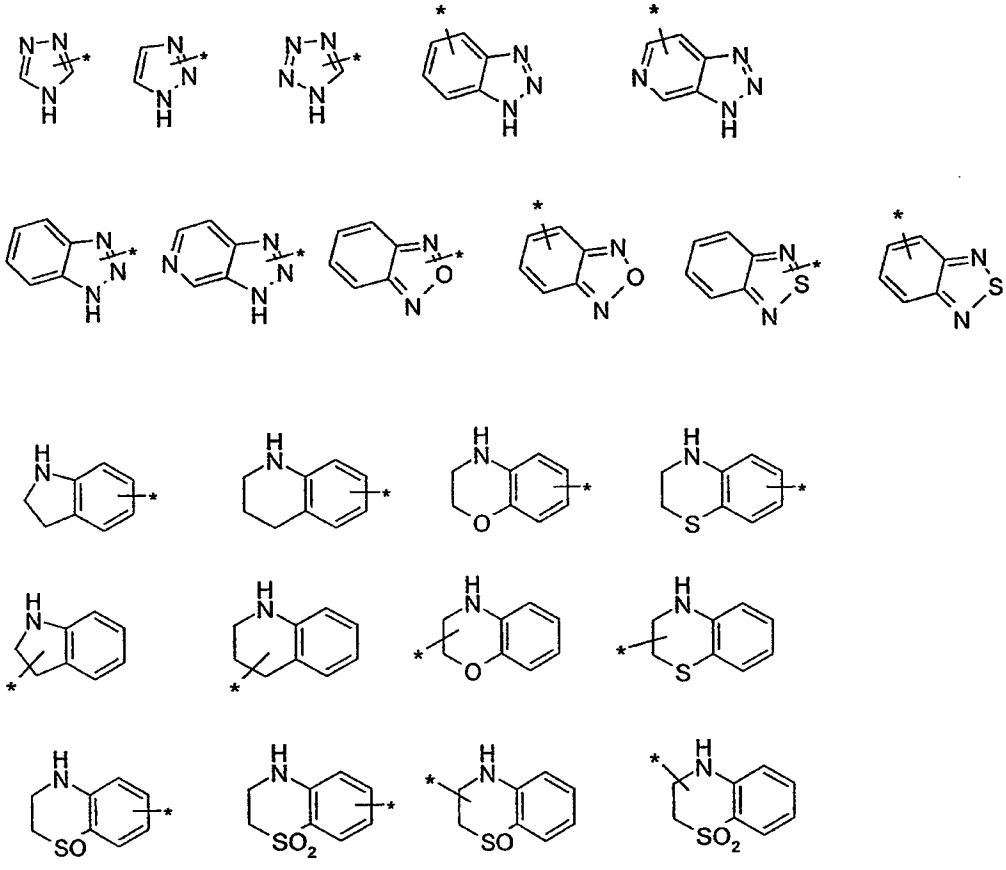
where any phenyl or naphthyl or mono- or bicyclic heterocyclyl (which mono- or bicyclic heterocyclyl is preferably as defined for mono- or bicyclic heterocyclyl, more preferably is selected from pyrrolyl, furanyl, tetrahydrofuranyl, tetrahydropyranyl and thienyl) mentioned as substituent of or as part of a substituent of substituted aryl is unsubstituted or substituted by one or more, preferably up to three, moieties independently selected from the group consisting of C_1-C_7-alkyl, C_1-C_7-alkenyl, C_1-C_7-alkynyl, halo-C_1-C_7-alkyl, such as trifluoromethyl, halo, especially fluoro, chloro, bromo or iodo, hydroxy, C_1-C_7-alkoxy, phenyloxy, naphthyloxy, phenyl- or naphthyl-C_1-C_7-alkoxy, C_1-C_7-alkanoyloxy, phenyl- or naphthyl-C_1-C_7-alkanoyloxy, amino, mono- or di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl, C_1-C_7-alkanoyl and/or phenyl- or naphthyl-C_1-C_7-alkanoyl)-amino, carboxy, C_1-C_7-alkoxycarbonyl, phenoxycarbonyl, naphthyloxycabonyl, phenyl-C_1-C_7-alkyloxycarbonyl, naphthyl-C_1-C_7-alkoxycarbonyl, carbamoyl, N-mono- or N,N-di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-aminocarbonyl, cyano, sulfo, sulfamoyl, N-mono- or N,N-di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-aminosulfonyl and nitro, or preferably, where preferred substituents are mentioned, by one or more of these mentioned substituents;

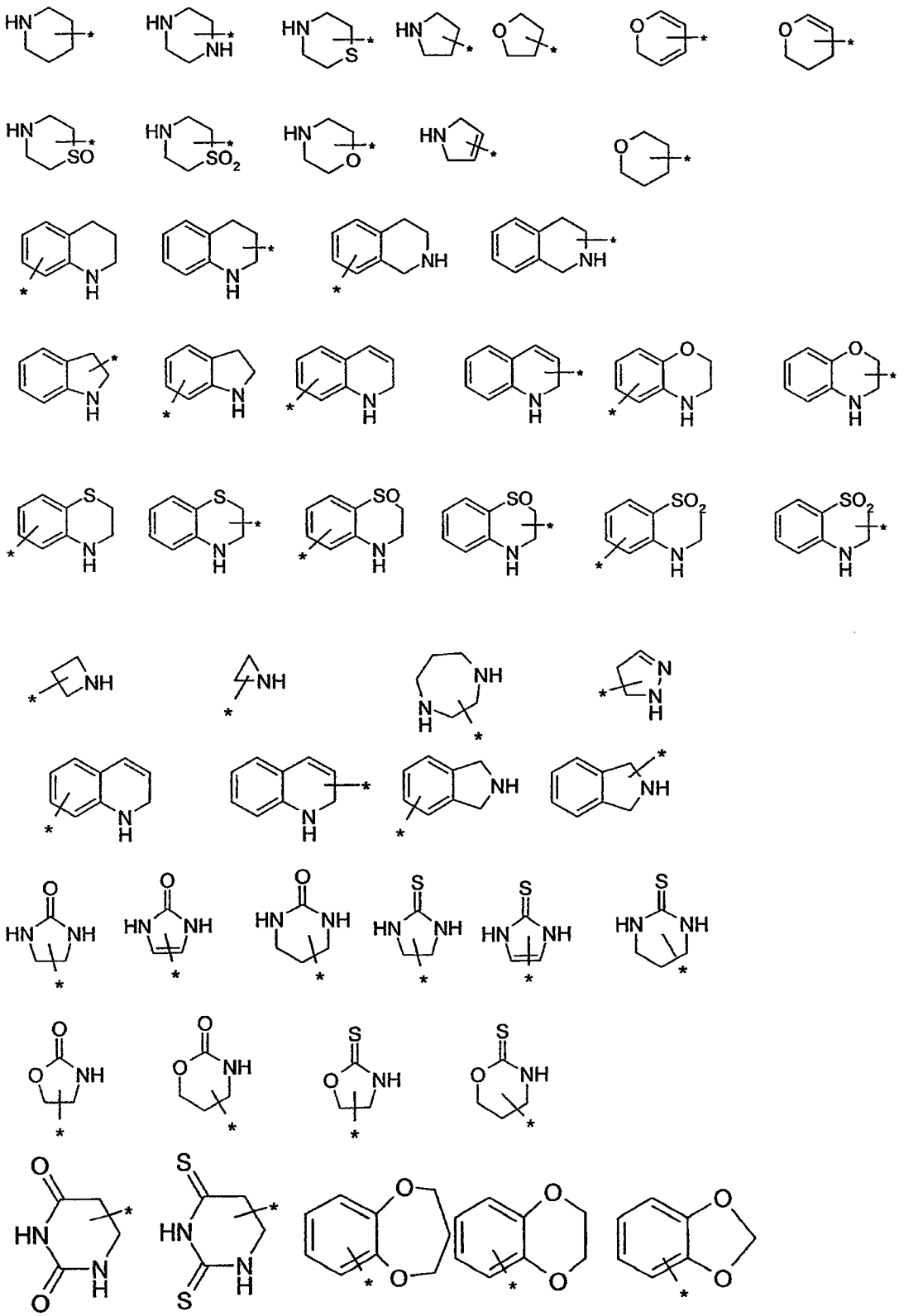
unsubstituted or substituted mono- or bicyclic heterocyclyl is a mono- or bicyclic heterocyclic moiety with an unsaturated, partially saturated or saturated ring system with preferably 3 to 22, more preferably 3 to 14, ring atoms and with one or more, preferably one to four, heteroatoms independently selected from nitrogen, oxygen and sulfur, which is unsubstituted or substituted by one or more, e.g. up to three, substitutents preferably independently selected from the substitutents mentioned above for aryl and from oxo (=O), imino (=NR) where R can be C_1-C_7-alkyl or hydrogen, and thioxo (=S), preferably oxo (=O) and thioxo (=S), where preferably, unsubstituted or substituted mono- or bicyclic heterocyclyl is selected from the following moieties:

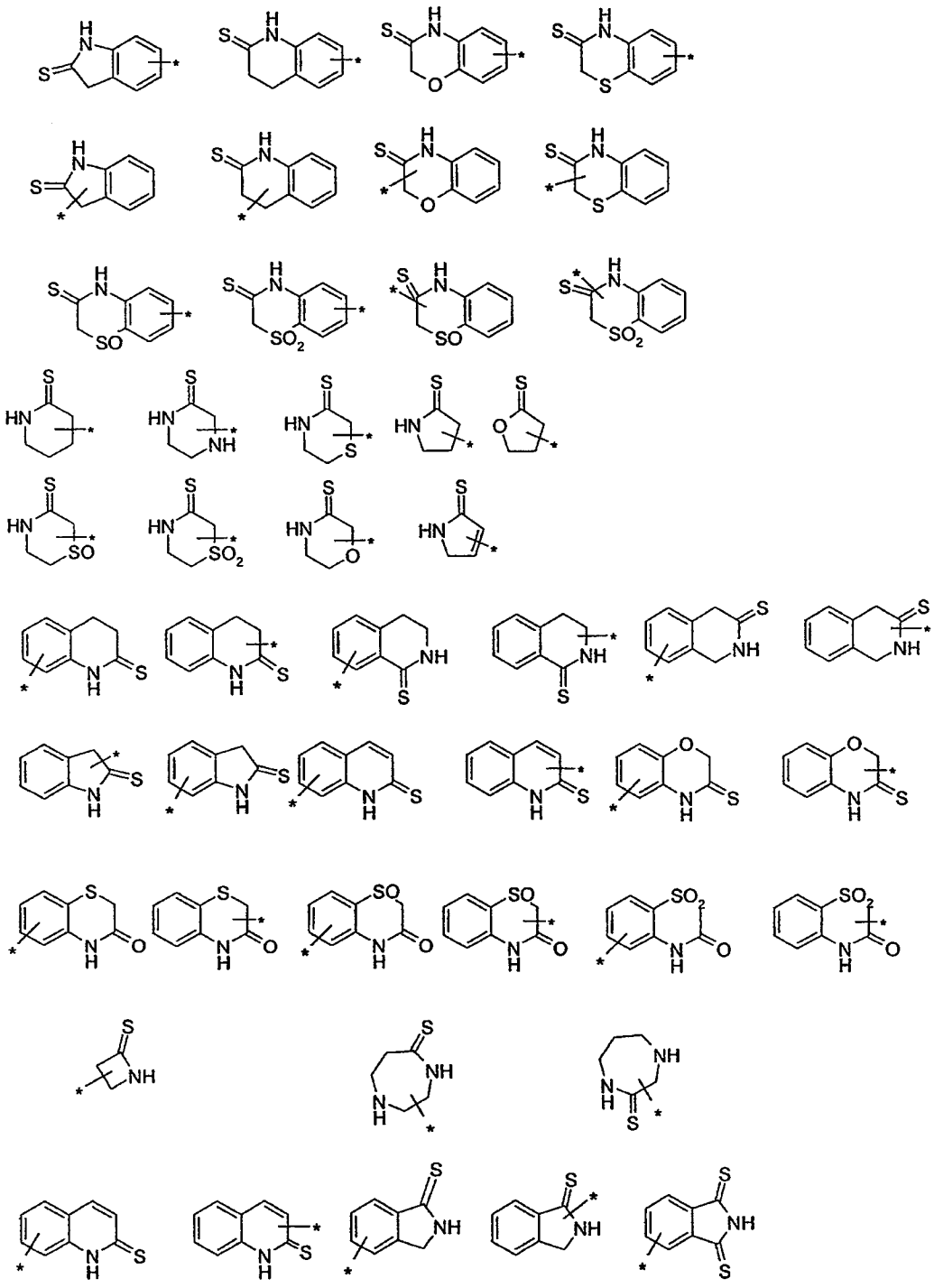


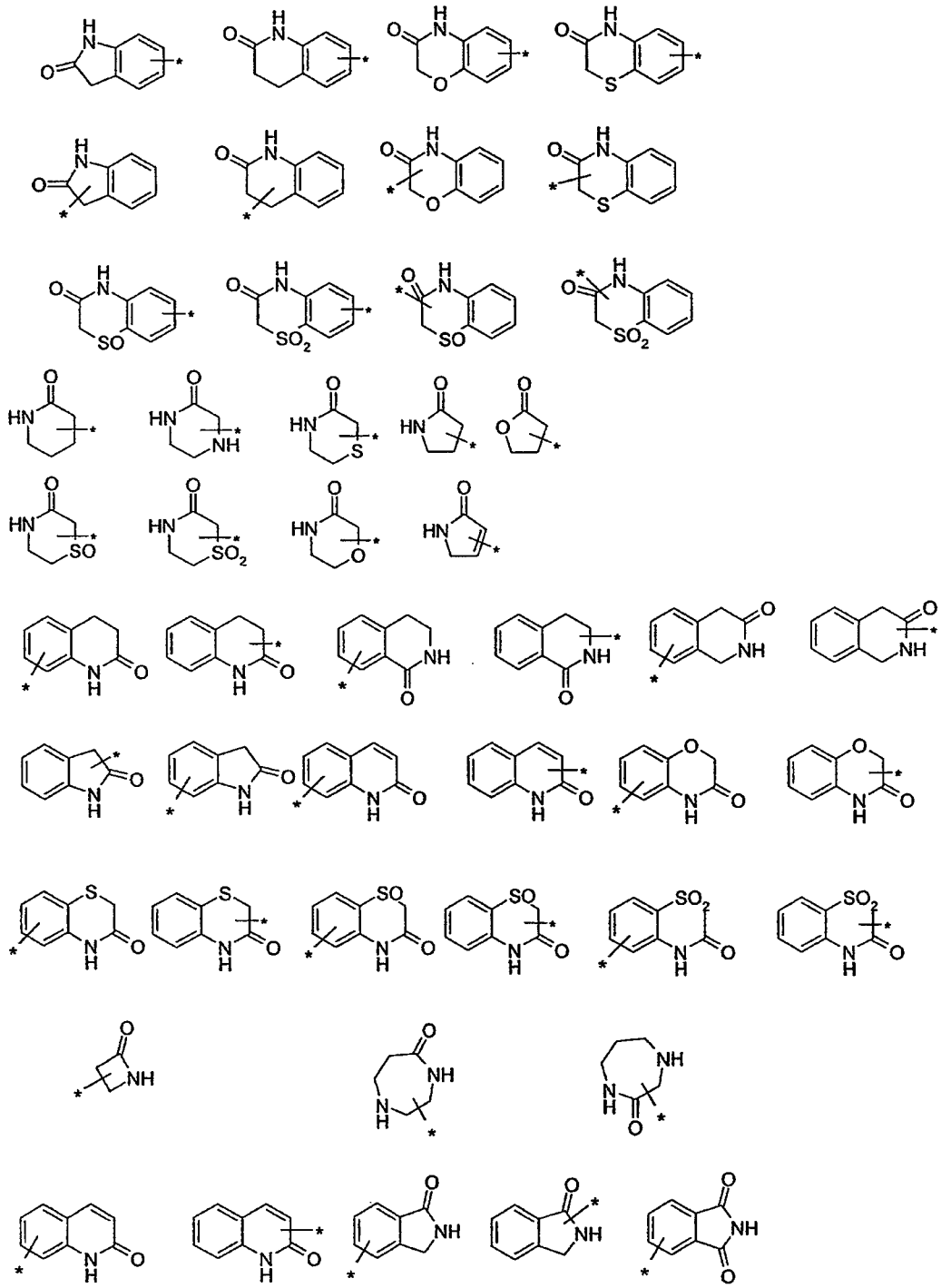












where in each case where an NH is present the bond with the asterisk connecting the respective heterocyclyl moiety to the rest of the molecule the H may be replaced with said

bond and/or the H may be replaced by a substituent (thus forming substituted imino), and one or more substituents may be present as just described;

unsubstituted or substituted mono- or bicyclic cycloalkyl is mono- or bicyclic, more preferably monocyclic, C_3-C_{16}, more preferably C_3-C_{10}-cycloalkyl, which may include one or more double (e.g. in cycloalkenyl) and/or triple bonds (e.g. in cycloalkinyl) with less double and/or triple bonds than required to form a fully unsaturated ring system; where preferably, mono- or bicyclic cycloalkyl is saturated; and where the mono- or bicyclic cycloalkyl is unsubstituted or substituted by one or more, e.g. one to three substitutents preferably independently selected from those mentioned above as substituents for aryl;

in unsubstituted or substituted mono- or bicyclic aryl-alkyl or –C_1-C_7-alkyl, mono- or bicyclic aryl which is unsubstituted or substituted by one or more substituents, e.g. one to three substituents independently selected from those mentioned above as substituents for aryl and aryl is bound to alkyl, preferably C_1-C_7-alkyl, either terminally or at any other carbon in the alkyl chain, e.g. at the 1-carbon; where the C_1-C_7-alkyl is otherwise unsubstituted or substituted as described below for unsubstituted or substituted alkyl and/or with unsubstituted or substituted mono- or bicyclic aryl as described above;

in unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl or –C_1-C_7-alkyl, mono- or bicyclic heterocyclyl is preferably as described above and is unsubstituted or substituted by one or more, e.g. up to three, substitutents independently selected from those mentioned above for substituted aryl, and from oxo (=O), imino (=NR) where R can be C_1-C_7-alkyl or hydrogen, and thioxo (=S), preferably oxo (=O) and thioxo (=S), and heterocyclyl is bound to alkyl, preferably C_1-C_7-alkyl, either terminally or at any other carbon in the alkyl chain, e.g. at the 1-carbon; where the C_1-C_7-alkyl is otherwise unsubstituted or substituted as described below for unsubstituted or substituted alkyl and/or with unsubstituted or substituted mono- or bicyclic aryl as described above;

in unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or –C_1-C_7-alkyl, mono- or bicyclic cycloalkyl is preferably as described above and is unsubstituted or substituted by one or more, e.g. up to three, substitutents independently selected from those mentioned above for substituted aryl, and cycloalkyl is bound to alkyl, preferably C_1-C_7-alkyl, either terminally or at any other carbon in the alkyl chain, e.g. at the 1-carbon; where the C_1-C_7-

alkyl is otherwise unsubstituted or substituted as described below for unsubstituted or substituted alkyl and/or with unsubstituted or substituted mono- or bicyclic aryl as described above;

acyl is preferably unsubstituted or substituted mono- or bicyclic aryl-carbonyl or -sulfonyl, unsubstituted or substituted mono- or bicyclic heterocyclylcarbonyl or -sulfonyl, unsubstituted or substituted mono- or bicyclic cycloalkylcarbonyl or -sulfonyl, formyl or (unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkyl or unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkyl)-carbonyl or -sulfonyl, or - especially if bound to N, S or O - unsubstituted or substituted alkyloxycarbonyl, unsubstituted or substituted mono- or bicyclic aryl-oxycarbonyl, unsubstituted or substituted mono- or bicyclic heterocyclyloxycarbonyl, unsubstituted or substituted mono- or bicyclic cyclo-alkyloxycarbonyl, unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-oxycarbonyl , unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-oxycarbonyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-oxycarbonyl or N-mono- or N,N-di-(unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkyl and/or unsubstituted or substituted alkyl)-aminocarbonyl or -aminosulfonyl, with the proviso that–oxycarbonyl bound moieties are preferably bound to a nitrogen in the rest of the molecule; where preferred acyl moieties other than R^1 and/or R^2 where mentioned are C_1-C_7-alkanoyl, unsubstituted or (mono-, di- or tri-(halo, C_1-C_7-alkoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyl and/or C_1-C_7-alkyl)-substituted)-phenyl-C_1-C_7-alkanoyl, C_3-C_8-cycloalkyl-carbonyl or C_3-C_8-cycloalkyl-C_1-C_7-alkyl-carbonyl, (tetrahydrofuranyl or tetrahydropyranyl)-carbonyl or (tetrahydrofuranyl or tetrahydropyranyl)-C_1-C_7-alkyl-carbonyl, unsubstituted or mono-, di- or tri-(halo and/or C_1-C_7-alkyl)-substituted) (phenyl- or phenyl-C_1-C_7-alkyl)-sulfonyl, C_1-C_7-alkylsulfonyl, N-mono- or N,N-di-(C_1-C_7-alkyl)-aminocarbonyl, N-[phenyl or phenyl-C_1-C_7-alkyl]-aminocarbonyl, N-[C_3-C_8-cycloalkyl or C_3-C_8-cycloalkyl-C_1-C_7-alkyl]aminocarbonyl, C_1-C_7-alkylaminocarbonyl, N-(phenyl-C_1-C_7-alkyl)(C_1-C_7-alkyl)-aminocarbonyl, N-(phenyl-C_1-C_7-alkyl)(C_3-C_8-cycloalkyl-C_1-C_7-alkyl)-aminocarbonyl, N-(C_1-C_7-alkyl)(C_3-C_8-cycloalkyl-C_1-C_7-alkyl)-aminocarbonyl, N-(phenyl-C_1-C_7-alkyl)(C_3-C_8-cycloalkyl)-aminocarbonyl, N-(heterocyclyl-C_1-C_7-alkyl)(C_3-C_8-cycloalkyl)-aminocarbonyl, N-

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(heterocyclyl)(C_3-C_8-cycloalkyl)-aminocarbonyl, or (C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl, napthyl-C_1-C_7-alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-C_1-C_7-alkyl, mono- or bicyclic heterocyclyl-C_1-C_7-alkyl and/or mono- or bicyclic heterocyclyl selected preferably from pyrrolyl, furanyl, thienyl (= thiophenyl), thiazolyl, pyrazolyl, triazolyl, tetrazolyl, oxetidinyl, 3-(C_1-C_7-alkyl)-oxetidinyl, pyridyl, pyrimidinyl, morpholino, thiomorpholino, piperidinyl, piperazinyl, pyrrolidinyl, 1H-indazanyl, benzofuranyl, benzothiophenyl, (more preferably) isoquinolinyl, quinolinyl, tetrahydrofuran-onyl, tetrahydro-pyranyl, indolyl)-oxycarbonyl, and (tetrahydrofuranyl or tetrahydropyranyl)- C_1-C_7-alkyl oxycarbonyl, while as preferred acyl R^1 or R^2, indolyl-C_1-C_7-alkanoyl, -2,3-dihydro-benzo[1,4]dioxine-carbonyl, quinolyl-C_1-C_7-alkanoyl or phenyl-C_1-C_7-alkanoyl, wherein indolyl, 2,3-dihydro-benzo[1,4]dioxine, quinolyl and phenyl are unsubstituted or substituted by a substituent of the formula -(C_0-C_7-alkylene)-$(X)_r$-(C_1-C_7-alkylene)-$(Y)_s$-(C_0-C_7-alkylene)-H where C_0-alkylene means that a bond is present instead of bound alkylene, alkylene in each case may be straight-chained or branched and unsubstituted or substituted e.g. by one or more moieties as defined for substituted alkyl, especially by halo, especially fluoro, hydroxy, C_1-C_7-alkoxy, phenyloxy, naphthyloxy, C_1-C_7-alkanoyloxy, benzoyloxy, naphthoyloxy, amino, mono- or di-(C_1-C_7-alkyl, C_1-C_7-alkanoyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-amino, carboxy, C_1-C_7-alkoxycarbonyl or cyano, r and s, each independently of the other, are 0 or 1 and each of X and Y, if present and independently of the others, is -O-, -NV-, -S-, -O-CO-, -CO-O-, -NV-CO-; -CO-NV-; -NV-SO_2-, -SO_2-NV; -NV-CO-NV-, -NV-CO-O-, -O-CO-NV-, -NV-SO_2-NV- wherein V is hydrogen or unsubstituted or substituted alkyl as defined below, especially C_1-C_7-alkyl, or is phenyl, naphthyl, phenyl- or naphthyl-C_1-C_7-alkyl or halo-C_1-C_7-alkyl; and optionally one or more, e.g. up to two, further substituents selected from the other substituents mentioned above for substituted aryl; where unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl and unsubstituted or substituted mono- or bicyclic cycloalkyl are preferably as defined above whereever they are mentioned as part of acyl, while unsubstituted or substituted alkyl is preferably as defined below;

unsubstituted or substituted alkyl is C_1-C_{20}-alkyl, more preferably C_1-C_7-alkyl, that is straight-chained or branched (one or, where appropriate, more times), which is unsubstituted or substituted by one or more, e.g. up to three moieties selected from unsubstituted or substituted mono- or bicyclic heterocyclyl as described below, especially pyrrolyl, furanyl, thienyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, oxetidinyl, 3-(C_1-C_7-alkyl)-oxetidinyl, pyridyl, pyrimidinyl, morpholino, thiomorpholino, piperidinyl, piperazinyl, pyrrolidinyl, tetrahydrofuran-

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onyl, tetrahydro-pyranyl, 1H-indazanyl, benzofuranyl, benzothiophenyl, isoquinolinyl, quinolinyl or especially indolyl, each of which is unsubstituted or substituted as described above for unsubstituted or substituted heterocyclyl, e.g. by one to three substitutents independently selected from halo, hydroxy, C_1-C_7-alkyl, cyano and C_1-C_7-alkanoyl; from unsubstituted or substituted mono- or bicyclic cycloalkyl as described above, especially cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl each of which is unsubstituted or substituted as described below for unsubstituted or substituted cycloalkyl; or especially from the group consisting of C_2-C_7-alkenyl, C_2-C_7-alkinyl, halo, hydroxy, C_1-C_7-alkoxy, halo-C_1-C_7-alkoxy, such as trifluoromethoxy, hydroxy-C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, phenyl- or naphthyloxy, phenyl- or naphthyl-C_1-C_7-alkyloxy, C_1-C_7-alkanoyloxy, (C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, phenyl and/or phenyl-C_1-C_7-alkyl)-aminocarbonyloxy, benzoyl- or naphthoyloxy, C_1-C_7-alkylthio, halo-C_1-C_7-alkthio, hydroxy-C_1-C_7-alkylthio, C_1-C_7-alkoxy-C_1-C_7-alkylthio, phenyl- or naphthylthio, phenyl- or naphthyl-C_1-C_7-alkylthio, nitro, amino, mono- or di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl and/or C_1-C_7-alkoxy-C_1-C_7-alkyl)-amino, C_1-C_7-alkanoylamino, benzoyl- or naphthoylamino, C_1-C_7-alkylsulfonylamino, phenyl- or naphthylsulfonylamino, phenyl- or naphthyl-C_1-C_7-alkylsulfonylamino, C_1-C_7-alkyl moieties, phenyl- or naphthyl-C_1-C_7-alkylcarbonylamino, carboxyl, C_1-C_7-alkyl-carbonyl, C_1-C_7-alkoxy-carbonyl, phenyl- or naphthyloxycarbonyl, phenyl- or naphthyl-C_1-C_7-alkoxycarbonyl, carbamoyl, N- mono- or N,N-di-(C_1-C_7-alkyl)-aminocarbonyl, N-mono- or N,N-di-(naphthyl- or phenyl-C_1-C_7-alkyl)-aminocarbonyl, cyano, sulfenyl, sulfonyl, C_1-C_7-alkylsulfinyl, phenyl- or naphthylsulfinyl moieties, phenyl- or naphthyl-C_1-C_7-alkylsulfinyl, sulfonyl, C_1-C_7-alkylsulfonyl, phenyl- or naphthylsulfonyl, phenyl- or naphthyl-C_1-C_7-alkylsulfonyl, sulfamoyl, N-mono or N,N-di-(C_1-C_7-alkyl, phenyl-, naphthyl, phenyl-C_1-C_7-alkyl or naphthyl-C_1-C_7-alkyl)-aminosulfonyl, N-mono-, N'-mono-, N,N-di- or N,N,N'-tri-(C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, phenyl and/or phenyl-C_1-C_7-alkyl)-aminocarbonylamino or –aminocarbonyloxy and N-mono-, N'-mono-, N,N-di- or N,N,N'-tri-(C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl and/or C_1-C_7-alkoxy-C_1-C_7-alkyl) aminosulfonylamino;

where any phenyl or naphthyl mentioned as substituent of or as part of a substituent of substituted alkyl is unsubstituted or substituted by one or more, preferably up to three, moieties independently selected from the group consisting of C_1-C_7-alkyl, C_1-C_7-alkenyl, C_1-C_7-alkynyl, halo-C_1-C_7-alkyl, such as trifluoromethyl, halo, especially fluoro, chloro, bromo or iodo, hydroxy, C_1-C_7-alkoxy, phenyloxy, naphthyloxy, phenyl- or naphthyl-C_1-C_7-alkoxy, C_1-C_7-alkanoyloxy, phenyl- or naphthyl-C_1-C_7-alkanoyloxy, amino, mono- or di-(C_1-C_7-alkyl,

phenyl, naphthyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl, C_1-C_7-alkanoyl and/or phenyl- or naphthyl-C_1-C_7-alkanoyl)-amino, carboxy, C_1-C_7-alkoxycarbonyl, phenoxycarbonyl, naphthyloxycabonyl, phenyl-C_1-C_7-alkyloxycarbonyl, naphthyl-C_1-C_7-alkoxycarbonyl, carbamoyl, N-mono- or N,N-di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-aminocarbonyl, cyano, sulfo, sulfamoyl, N-mono- or N,N-di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-aminosulfonyl and nitro, or preferably, where preferred substituents are mentioned, by one or more of these mentioned substituents;

unsubstituted or substituted alkenyl is preferably C_2-C_{20}-alkenyl, more preferably C_2-C_7-alkenyl with one or, if possible, more double bonds, that is straight-chained or branched one or, where appropriate, more times, which is unsubstituted or substituted by one or more, e.g. up to three moieties selected from those mentioned as substituents for subsituted alkyl and from unsubsituted or substituted mono- or bicyclic aryl, each as described above;

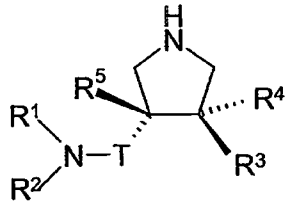
unsubstituted or substituted alkynyl is preferably C_2-C_{20}-alkynyl, more preferably C_2-C_7-alkynyl with one or, if possible, more triple bonds, that is straight-chained or branched one or, where appropriate, more times, which is unsubstituted or substituted by one or more, e.g. up to three moieties selected from those mentioned as substituents for subsituted alkyl and from unsubsituted or substituted mono- or bicyclic aryl,;

esterified hydroxy is preferably acyloxy with acyl as defined above, more preferably C_1-C_7-alkanoyloxy or benzoyloxy;

etherified hydroxy is unsubstituted or preferably substituted C_1-C_7-alkyloxy wherein substituted alkyl is preferably as defined above, unsubstituted or substituted mono- or bicyclic aryloxy, unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyloxy, unsubstituted or substituted mono- or bicyclic heterocyclyloxy, unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkyloxy, unsubstituted or substituted mono- or bicyclic cycloalkyloxy or unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkyloxy, where in each case the moieties are preferably defined as above, or more preferably unsubstituted alkyloxy, especially C_1-C_7-alkyloxy; and

the 3 to 7 membered nitrogen containing ring formed by R_b and R_c which can be unsubstituted or substituted is a fully saturated, partially unsaturated or aromatic hydrocarbon ring, preferably a fully saturated hydrocarbon ring, and is preferably unsubstituted or substituted by one or more, e.g. one to four substitutents preferably independently selected from those mentioned above as substituents for aryl, especially a 4- to 7-membered ring that is unsubstituted or substituted by up to four substituents, such as one substituent, selected from hydroxy, halo, such as chloro, C_1-C_7-alkyl, such as methyl, cyano, hydroxy-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, C_1-C_7-alkanoyl, such as acetyl, C_1-C_7-alkoxy, halo-C_1-C_7-alkoxy, such as trifluoromethoxy, hydroxy-C_1-C_7-alkoxy, and C_1-C_7-alkoxy-C_1-C_7-alkoxy; preferably a pyrrolidine or piperidine ring is formed by R_b and R_c that is substituted by up to four moieties selected from C_1-C_7-alkyl, hydroxyl, halo, hydroxy-C_1-C_7-alkyl, halo-C_1-C_7-alkyl and cyano, or is preferably unsubstituted.

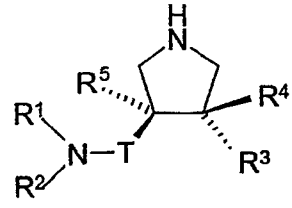
8. The use according to any one of claims 1 to 3 or 7, the compound of the formula I or a pharmaceutically acceptable salt thereof for use according to claim 4 or 7, or the compound of formula I or a salt thereof according to any one of claims 5 to 7, wherein formula I has the configuration given in formula IA



(IA);

wherein R^1, R^2, R^3, R^4, R^5 and T are as described in any one of the referenced claims.

9. The use according to any one of claims 1 to 3 or 7, the compound of the formula I or a pharmaceutically acceptable salt thereof for use according to claim 4 or 7, or the compound of formula I or a salt thereof according to any one of claims 5 to 7, wherein formula I has the configuration given in formula IB



(IB);

wherein R^1, R^2, R^3, R^4, R^5 and T are as described in any one of the referenced claims.

10. The use according to claim 1 of a compound of the formula I, wherein
R^1 is phenyl, naphthyl, mono- or bicyclic heterocyclyl, phenylcarbonyl, phenylacetyl, naphthylcarbonyl, naphthylacetyl, mono- or bicyclic heterocyclylcarbonyl or -acetyl, phenylsulfonyl, naphthylsulfonyl or mono- or bicyclic heterocyclylsulfonyl; wherein mono- or bicyclic heterocyclyl is pyrrolyl, furanyl, thienyl thiazolyl, pyrazolyl, triazolyl, tetrazolyl, oxetidinyl, 3-(C_1-C_7-alkyl)-oxetidinyl, pyridyl, pyrimidinyl, morpholino, thiomorpholino, piperidinyl, piperazinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrofuran-onyl, tetrahydro-pyranyl, 1H-indazolyl, benzofuranyl, benzothiophenyl or more preferably isoquinolyl, quinolyl or especially indolyl or -2,3-dihydro-benzo[1,4]dioxine, and each such mono- or bicyclic heterocyclyl, phenyl or naphthyl mentioned is unsubstituted or preferably substituted by one or more, especially one to three, moieties, preferably independently selected from the group consisting of
(i) a substituent of the formula -(C_0-C_7-alkylene)-$(X)_r$-(C_1-C_7-alkylene)-$(Y)_s$-(C_0-C_7-alkylene)-H where C_0-alkylene means that a bond is present instead of bound alkylene, alkylene in each case may be straight-chained or branched and unsubstituted or substituted e.g. by one or more moieties as defined for substituted alkyl, especially by halo, especially fluoro, hydroxy, C_1-C_7-alkoxy, phenyloxy, naphthyloxy, C_1-C_7-alkanoyloxy, benzoyloxy, naphthoyloxy, amino, mono- or di-(C_1-C_7-alkyl, C_1-C_7-alkanoyl, phenyl-C_1-C_7-alkanoyl, naphthyl-C_1-C_7-alkanoyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-amino, carboxy, C_1-C_7-alkoxycarbonyl or cyano, r and s, each independently of the other, are 0 or 1 and each of X and Y, if present and independently of the others, is -O-, -NV-, -S-, -O-CO-, -CO-O-, -NV-CO-; -CO-NV-; -NV-SO_2-, -SO_2-NV; -NV-CO-NV-, -NV-CO-O-, -O-CO-NV-, -NV-SO_2-NV- wherein V is hydrogen or unsubstituted or substituted alkyl as defined below, especially C_1-C_7-alkyl, or is phenyl, naphthyl, phenyl- or naphthyl-C_1-C_7-alkyl or halo-C_1-C_7-alkyl; e.g. C_1-C_7-alkyl, halo-C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkoxy-C_1-C_7-alkyl, phenyloxy- or naphthyloxy-C_1-C_7-alkyl, C_1-C_7-alkanoyloxy-C_1-C_7-alkyl, amino-C_1-C_7-alkyl, such as aminomethyl, C_1-C_7-alkoxy-C_1-C_7-alkylamino-C_1-C_7-alkyl, mono- or di- (C_1-C_7-alkyl-, naphthyl-, phenyl, naphthyl-C_1-C_7-alkyl and/or phenyl-C_1-C_7-alkyl)-amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino-C_1-C_7-alkyl, C_1-C_7-alkyl-O-CO-NH-C_1-C_7-alkyl, C_1-C_7-alkylsulfonylamino-C_1-C_7-alkyl, C_1-C_7-alkyl-NH-CO-NH-C_1-C_7-alkyl, C_1-C_7-alkyl-NH-SO_2-NH-C_1-C_7-alkyl, C_1-C_7-alkoxy, hydroxy-C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, C_1-C_7-alkanoyloxy, halo-C_1-C_7-alkoxy, such as trifluoromethoxy, phenyl- or naphthyl-C_1-C_7-

alkanoyloxy, phenyl- or naphthyl-C_1-C_7-alkylaminocarbonyloxy, halo-C_1-C_7-alkylthio, phenyl- or naphthyl-C_1-C_7-alkylthio, mono- or di-(C_1-C_7-alkyl-, naphthyl-C_1-C_7-alkyl-, phenyl-C_1-C_7-alkyl- and/or C_1-C_7-alkoxy-C_1-C_7-alkyl-)amino, C_1-C_7-alkanoylamino, C_1-C_7-alkylsulfonylamino, phenyl- or naphthyl-C_1-C_7-alkanoylamino, phenyl- or naphthyl-C_1-C_7-alkylaminocarbonylamino, carboxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-carbonyl, hydroxy-C_1-C_7-alkoxycarbonyl, C_1-C_7-alkoxy-C_1-C_7-alkoxycarbonyl, amino-C_1-C_7-alkoxycarbonyl, (N-) mono-(C_1-C_7-alkyl)-amino-C_1-C_7-alkoxycarbonyl, C_1-C_7-alkanoylamino-C_1-C_7-alkoxycarbonyl, N-mono- or N,N-di-(C_1-C_7-alkyl, naphthyl-C_1-C_7.alkyl and/ or phenyl-C_1-C_7-alkyl)-aminocarbonyl, C_1-C_7-alkylsulfonyl, halo-C_1-C_7-alkylsulfonyl, hydroxy-C_1-C_7-alkylsulfonyl, C_1-C_7-alkoxy-C_1-C_7-alkylsulfonyl, amino-C_1-C_7-alkylsulfonyl, N-mono- or di-(C_1-C_7-alkyl)-amino-C_1-C_7-alkylsulfonyl, C_1-C_7-alkanoylamino-C_1-C_7-alkylsulfonyl, N-C_1-C_7-alkoxy-C_1-C_7-alkylcarbamoyl or N-mono- or N,N-di-(C_1-C_7-alkyl)-aminosulfonyl,

(ii) from C_2-C_7-alkenyl, C_2-C_7-alkynyl, phenyl, naphthyl, mono- or bicyclic heterocyclyl, especially as defined below for mono- or bicyclic heterocyclyl, preferably selected from pyrrolyl, furanyl, thienyl, pyrimidine-2,4-dione-1-, -3- or –5-yl, tetrahydropyranyl and tetrahydrofuranyl, phenyl- or naphthyl- or (mono- or bicyclic heterocyclyl)-C_1-C_7-alkyl or C_1-C_7-alkyloxy wherein mono- or bicyclic heterocyclyl is as defined below, preferably selected from pyrrolyl, furanyl, tetrahydrofuranyl, tetrahydropyranyl and thienyl; tetrahydrofuranyl- or tetrahydropyranyl-C_1-C_7-alkyloxycarbonyl, benzoyl- or naphthoylamino-C_1-C_7-alkyl, (phenyl- or naphthyl- or mono- or bicyclic heterocyclyl)-sulfonylamino-C_1-C_7-alkyl, wherein phenyl or naphthyl or mono- or bicyclic heterocyclyl is unsubstituted or substituted, preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkylsulfonylamino-C_1-C_7-alkyl, halo, hydroxy, phenyl-C_1-C_7-alkoxy wherein phenyl is preferably unsubstituted or substituted, preferably by C_1-C_7-alkoxy and/or halo, mono- or bicyclic heterocyclyl-C_1-C_7-alkoxy, (mono- or bicyclic heterocyclyl or phenyl or naphthyl)-oxy, naphthyl-C_1-C_7-alkyloxy, benzoyl or naphthoyl or mono- or bicyclic heterocyclylcarbonyl)-oxy, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-aminocarbonyloxy, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-thio, (benzoyl or naphthoyl or mono- or bicyclic heterocyclyl)-thio, nitro, amino, di-((naphthyl or phenyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkyl)-amino, (benzoyl or naphthoyl or mono- or bicyclic heterocyclyl)-amino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-sulfonylamino wherein phenyl or naphthyl is unsubstituted or substituted preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkylsulfonylamino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-

aminocarbonylamino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-oxycarbonylamino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkyloxycarbonylamino, carboxyl, C_1-C_7-alkyl-carbonyl, halo-C_1-C_7-alkylcarbonyl, hydroxy-C_1-C_7-alkylcarbonyl, C_1-C_7-alkoxy-C_1-C_7-alkylcarbonyl, amino-C_1-C_7-alkylcarbonyl, (N-) mono- or (N,N-) di-(C_1-C_7-alkyl)-amino-C_1-C_7-alkylcarbonyl, C_1-C_7-alkanoylamino-C_1-C_7-alkylcarbonyl, halo-C_1-C_7-alkoxycarbonyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-oxy-carbonyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkoxycarbonyl, (N,N-) di-(C_1-C_7-alkyl)-amino-C_1-C_7-alkoxycarbonyl, carbamoyl, N-mono or N,N-di-(naphthyl or phenyl or mono- or bicyclic heterocyclyl)-aminocarbonyl, cyano, C_1-C_7-alkylene which is unsubstituted or substituted by up to four C_1-C_7-alkyl substituents and bound to two adjacent ring atoms of the aryl moiety, sulfenyl, sulfinyl, C_1-C_7-alkylsulfinyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-sulfinyl wherein phenyl or naphthyl is unsubstituted or substituted preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, phenyl- or naphthyl-C_1-C_7-alkylsulfinyl, sulfonyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-sulfonyl wherein phenyl or naphthyl is unsubstituted or substituted preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkylsulfonyl, sulfamoyl and N-mono or N,N-di-(C_1-C_7-alkyl, phenyl-, naphthyl, mono- or bicyclic heterocyclyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl and/or mono- or bicyclic heterocyclyl-C_1-C_7-alkyl)-aminosulfonyl;

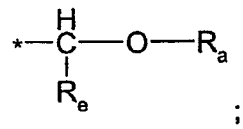
where any phenyl or naphthyl or mono- or bicyclic heterocyclyl - which mono- or bicyclic heterocyclyl is preferably as defined for mono- or bicyclic heterocyclyl, more preferably is selected from pyrrolyl, furanyl, tetrahydrofuranyl, tetrahydropyranyl and thienyl - mentioned as substituent of or as part of a substituent of mono- or bicyclic heterocyclyl, phenyl or naphthyl R^1 under (i) or (ii) is unsubstituted or substituted by one or more, preferably up to three, moieties independently selected from the group consisting of C_1-C_7-alkyl, C_1-C_7-alkenyl, C_1-C_7-alkynyl, halo-C_1-C_7-alkyl, halo, hydroxy, C_1-C_7-alkoxy, phenyloxy, naphthyloxy, phenyl- or naphthyl-C_1-C_7-alkoxy, C_1-C_7-alkanoyloxy, phenyl- or naphthyl-C_1-C_7-alkanoyloxy, amino, mono- or di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl, C_1-C_7-alkanoyl and/or phenyl- or naphthyl-C_1-C_7-alkanoyl)-amino, carboxy, C_1-C_7-alkoxycarbonyl, phenoxycarbonyl, naphthyloxycabonyl, phenyl-C_1-C_7-alkyloxycarbonyl, naphthyl-C_1-C_7-alkoxycarbonyl, carbamoyl, N-mono- or N,N-di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-aminocarbonyl, cyano, sulfo, sulfamoyl, N-mono- or N,N-di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-

alkyl)-aminosulfonyl and nitro, or preferably, where preferred substituents are mentioned, by one or more of these mentioned substituents;

R^2 is phenyl, naphthyl, phenyl-C_1-C_7-alkyl or naphthyl-C_1-C_7-alkyl, wherein each phenyl or naphthyl mentioned so far in the definition of R^2 is unsubstituted or substituted as just described for substituted phenyl or naphthyl in the definition of R^1, or is preferably C_3-C_8-cycloalkyl or is C_1-C_7-alkyl that is unsubstituted or substituted by one or more, especially up to three, e.g. one or two, substituents independently selected from the group consisting of C_2-C_7-alkenyl, C_2-C_7-alkinyl, halo, hydroxy, C_1-C_7-alkoxy, halo-C_1-C_7-alkoxy, hydroxy-C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, phenyl- or naphthyloxy, phenyl- or naphthyl-C_1-C_7-alkyloxy, C_1-C_7-alkanoyloxy, (C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, phenyl and/or phenyl-C_1-C_7-alkyl)-aminocarbonyloxy, benzoyl- or naphthoyloxy, C_1-C_7-alkylthio, halo-C_1-C_7-alkthio, such as trifluoromethylthio, hydroxy-C_1-C_7-alkylthio, C_1-C_7-alkoxy-C_1-C_7-alkylthio, phenyl- or naphthylthio, phenyl- or naphthyl-C_1-C_7-alkylthio, nitro, amino, mono- or di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl and/or C_1-C_7-alkoxy-C_1-C_7-alkyl)-amino, C_1-C_7-alkanoylamino, benzoyl- or naphthoylamino, phenyl- or naphthyl-C_1-C_7-alkylcarbonylamino, C_1-C_7-alkylsulfonylamino, phenyl- or naphthylsulfonylamino wherein phenyl or naphthyl is unsubstituted or substituted by one or more, especially one to three, C_1-C_7-alkyl moieties, phenyl- or naphthyl-C_1-C_7-alkylsulfonylamino, carboxyl, C_1-C_7-alkyl-carbonyl, C_1-C_7-alkoxy-carbonyl, phenyl- or naphthyloxycarbonyl, phenyl- or naphthyl-C_1-C_7-alkoxycarbonyl, carbamoyl, N- mono- or N,N-di-(C_1-C_7-alkyl)-aminocarbonyl, N-mono- or N,N-di-(naphthyl- or phenyl-C_1-C_7-alkyl)-aminocarbonyl, cyano, sulfenyl, sulfonyl, C_1-C_7-alkylsulfinyl, phenyl- or naphthylsulfinyl wherein phenyl or naphthyl is unsubstituted or substituted by one or more, especially one to three, C_1-C_7-alkyl moieties, phenyl- or naphthyl-C_1-C_7-alkylsulfinyl, sulfonyl, C_1-C_7-alkylsulfonyl, phenyl- or naphthylsulfonyl wherein phenyl or naphthyl is unsubstituted or substituted by one or more, especially one to three, C_1-C_7-alkyl moieties, phenyl- or naphthyl-C_1-C_7-alkylsulfonyl, sulfamoyl, N-mono or N,N-di-(C_1-C_7-alkyl, phenyl-, naphthyl, phenyl-C_1-C_7-alkyl or naphthyl-C_1-C_7-alkyl)-aminosulfonyl, N-mono-, N'-mono-, N,N-di- or N,N,N'-tri-(C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, phenyl and/or phenyl-C_1-C_7-alkyl)-aminocarbonylamino or –aminocarbonyloxy and N-mono-, N'-mono-, N,N-di- or N,N,N'-tri-(C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl and/or C_1-C_7-alkoxy-C_1-C_7-alkyl) aminosulfonylamino; or is C_3-C_{10}-cycloalkyl or C_3-C_{10}-cycloalkyl-C_1-C_7-alkyl;

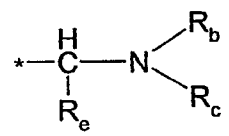
R^3 is a moiety selected from the group of moieties of the formulae

(a)

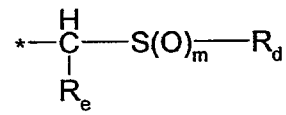


;

(b)

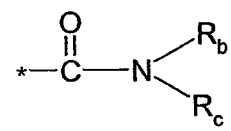


(c)



and

(f)



and

where in any of the moieties of the formulae given above under (a), (b), (c) and (f) the asterisk (*) shows the bond binding the respective moiety R^3 to the rest of the molecule in formula I,

R_a is acyl selected from C_1-C_7-alkanoyl, unsubstituted or mono-, di- or tri-(halo, C_1-C_7-alkoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyl and/or C_1-C_7-alkyl)-substituted) phenyl-C_1-C_7-alkanoyl, C_3-C_8-cycloalkylcarbonyl or C_3-C_8-cycloalkyl-C_1-C_7-alkyl-carbonyl, (tetrahydrofuranyl or tetrahydropyranyl)-carbonyl or (tetrahydrofuranyl or tetrahydropyranyl)-C_1-C_7-alkyl-carbonyl, N-mono- or N,N-di-(C_1-C_7-alkyl)-aminocarbonyl, N-[phenyl or phenyl-C_1-C_7-alkyl]-aminocarbonyl, N-[C_3-C_8-cycloalkyl or C_3-C_8-cycloalkyl-C_1-C_7-alkyl]-aminocarbonyl, C_1-C_7-alkylaminocarbonyl, N-(phenyl-C_1-C_7-alkyl)(C_1-C_7-alkyl)-aminocarbonyl, N-(phenyl-C_1-C_7-alkyl)(C_3-C_8-cycloalkyl-C_1-C_7-alkyl)-aminocarbonyl, N-(C_1-C_7-alkyl)(C_3-C_8-cycloalkyl-C_1-C_7-alkyl)-aminocarbonyl, N-(phenyl-C_1-C_7-alkyl)(C_3-C_8-cycloalkyl)-aminocarbonyl, N-(heterocyclyl-C_1-C_7-alkyl)(C_3-C_8-cycloalkyl)-aminocarbonyl, N-(heterocyclyl)(C_3-C_8-cycloalkyl)-aminocarbonyl; or is hydrogen;

R_b is C_1-C_7-alkyl or – in each case unsubstituted or substituted - phenyl, naphthyl, phenyl-C_1-C_7-alkyl or naphthyl-C_1-C_7-alkyl wherein in the case of a substituted moiety the substituents are one or more, especially up to three, substituents independently selected from the group consisting of C_1-C_7-alkyl, C_2-C_7-alkenyl, C_2-C_7-alkinyl, hydroxy-C_1-C_7-alkyl, halo-C_1-C_7-alkyl,

such as trifluoromethyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, amino-C_1-C_7-alkyl, C_1-C_7-alkoxy, hydroxy-C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, C_1-C_7-alkanoyloxy, amino, mono- or di-(C_1-C_7-alkyl)-amino, C_1-C_7-alkanoylamino, C_1-C_7-alkylsulfonylamino, C_1-C_7-alkoxy-carbonyl, carboxy-C_1-C_7-alkyl, halo, hydroxy, halo-C_1-C_7-alkoxy, halo-C_1-C_7-alkylthio, nitro, carboxyl, C_1-C_7-alkyl-carbonyl, halo-C_1-C_7-alkylcarbonyl, hydroxy-C_1-C_7-alkylcarbonyl, C_1-C_7-alkoxy-C_1-C_7-alkylcarbonyl, halo-C_1-C_7-alkoxycarbonyl, carbamoyl, cyano, C_1-C_7-alkylsulfinyl, sulfonyl, C_1-C_7-alkylsulfonyl, halo-C_1-C_7-alkylsulfonyl, hydroxy-C_1-C_7-alkylsulfonyl, C_1-C_7-alkoxy-C_1-C_7-alkylsulfonyl, sulfamoyl and N-mono or N,N-di-(C_1-C_7-alkyl) -aminosulfonyl; or is acyl e.g. as just defined under R_a, in particular C_1-C_7-alkanoyl, unsubstituted or (mono-, di- or tri-(halo, C_1-C_7-alkoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyl and/or C_1-C_7-alkyl)-substituted)-phenyl-C_1-C_7-alkanoyl, C_3-C_8-cycloalkyl-carbonyl or C_3-C_8-cycloalkyl-C_1-C_7-alkyl-carbonyl, (tetrahydrofuranyl or tetrahydropyranyl)-carbonyl or (tetrahydrofuranyl or tetrahydropyranyl)-C_1-C_7-alkyl-carbonyl, unsubstituted or mono-, di- or tri-(halo and/or C_1-C_7-alkyl)-substituted) (phenyl- or phenyl-C_1-C_7-alkyl)-sulfonyl, C_1-C_7-alkylsulfonyl, N-mono- or N,N-di-(C_1-C_7-alkyl)-aminocarbonyl, N-[phenyl or phenyl-C_1-C_7-alkyl]-aminocarbonyl, N-[C_3-C_8-cycloalkyl or C_3-C_8-cycloalkyl-C_1-C_7-alkyl]aminocarbonyl, C_1-C_7-alkylaminocarbonyl, N-(phenyl-C_1-C_7-alkyl)(C_1-C_7-alkyl)-aminocarbonyl, N-(phenyl-C_1-C_7-alkyl)(C_3-C_8-cycloalkyl-C_1-C_7-alkyl)-aminocarbonyl, N-(C_1-C_7-alkyl)(C_3-C_8-cycloalkyl-C_1-C_7-alkyl)-aminocarbonyl, N-(phenyl-C_1-C_7-alkyl)(C_3-C_8-cycloalkyl)-aminocarbonyl, N-(heterocyclyl-C_1-C_7-alkyl)(C_3-C_8-cycloalkyl)-aminocarbonyl, N-(heterocyclyl)(C_3-C_8-cycloalkyl)-aminocarbonyl, or (C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl, napthyl-C_1-C_7-alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-C_1-C_7-alkyl, mono- or bicyclic heterocyclyl-C_1-C_7-alkyl and/or mono- or bicyclic heterocyclyl selected preferably from pyrrolyl, furanyl, thienyl (= thiophenyl), thiazolyl, pyrazolyl, triazolyl, tetrazolyl, oxetidinyl, 3-(C_1-C_7-alkyl)-oxetidinyl, pyridyl, pyrimidinyl, morpholino, thiomorpholino, piperidinyl, piperazinyl, pyrrolidinyl, 1H-indazanyl, benzofuranyl, benzothiophenyl, (more preferably) isoquinolinyl, quinolinyl, tetrahydrofuran-onyl, tetrahydropyranyl, indolyl)-oxycarbonyl, and (tetrahydrofuranyl or tetrahydropyranyl)- C_1-C_7-alkyl oxycarbonyl, or selected from unsubstituted mono-, di- or tri-(halo and/or C_1-C_7-alkyl)-substituted (phenyl- or phenyl-C_1-C_7-alkyl)-sulfonyl, C_1-C_7-alkylsulfonyl;

R_c is hydroxy-C_1-C_7-alkyl or C_1-C_7-alkyloxy-C_1-C_7-alkyl, C_3-C_8-cycloalkyl C_1-C7-alkyl or preferably C_3-C_8-cycloalkyl, hydrogen or C_1-C_7-alkyl;

R_d is unsubstituted or substituted phenyl- or naphthyl-C_1-C_7-alkyl wherein in the case of a substituted moiety the substituents are one or more, especially up to three, substituents in-

dependently selected from those mentioned for unsubstituted of substituted phenyl- or naphthyl-C_1-C_7-alkyl under R_b, or is -$N(R_b)(R_c)$;
R_e is C_1-C_7-alkyl or preferably hydrogen; and
m is 2;

each of R^4 and R^5 is selected, independently from the other, from C_1-C_7-alkyl, hydroxy, C_1-C_7-alkyloxy and preferably hydrogen;
and T is carbonyl or preferably methylene;

or a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical formulation for the treatment of a disease that depends on activity of renin, especially hypertension.

11. A compound of the formula I according to claim 5, wherein
R^1 is phenyl, naphthyl, mono- or bicyclic heterocyclyl, phenylcarbonyl, phenylacetyl, naphthylcarbonyl, naphthylacetyl, mono- or bicyclic heterocyclylcarbonyl or -acetyl, phenylsulfonyl, naphthylsulfonyl or mono- or bicyclic heterocyclylsulfonyl; wherein mono- or bicyclic heterocyclyl is pyrrolyl, furanyl, thienyl thiazolyl, pyrazolyl, triazolyl, tetrazolyl, oxetidinyl, 3-(C_1-C_7-alkyl)-oxetidinyl, pyridyl, pyrimidinyl, morpholino, thiomorpholino, piperidinyl, piperazinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrofuran-onyl, tetrahydro-pyranyl, 1H-indazolyl, benzofuranyl, benzothiophenyl or more preferably isoquinolyl, quinolyl or especially indolyl or -2,3-dihydro-benzo[1,4]dioxine, and each such mono- or bicyclic heterocyclyl, phenyl or naphthyl mentioned is unsubstituted or preferably substituted by one or more, especially one to three, moieties, preferably independently selected from the group consisting of
(i) a substituent of the formula -(C_0-C_7-alkylene)-$(X)_r$-(C_1-C_7-alkylene)-$(Y)_s$-(C_0-C_7-alkylene)-H (especially in substituted aryl or substituted aryl-alkyl as R^1) where C_0-alkylene means that a bond is present instead of bound alkylene, alkylene in each case may be straight-chained or branched and unsubstituted or substituted e.g. by one or more moieties as defined for substituted alkyl, especially by halo, especially fluoro, hydroxy, C_1-C_7-alkoxy, phenyloxy, naphthyloxy, C_1-C_7-alkanoyloxy, benzoyloxy, naphthoyloxy, amino, mono- or di-(C_1-C_7-alkyl, C_1-C_7-alkanoyl, phenyl-C_1-C_7-alkanoyl, naphthyl-C_1-C_7-alkanoyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-amino, carboxy, C_1-C_7-alkoxycarbonyl or cyano, r and s, each independently of the other, are 0 or 1 and each of X and Y, if present and

independently of the others, is -O-, -NV-, -S-, -O-CO-, -CO-O-, -NV-CO-; -CO-NV-; -NV-SO_2-, -SO_2-NV; -NV-CO-NV-, -NV-CO-O-, -O-CO-NV-, -NV-SO_2-NV- wherein V is hydrogen or unsubstituted or substituted alkyl as defined below, especially C_1-C_7-alkyl, or is phenyl, naphthyl, phenyl- or naphthyl-C_1-C_7-alkyl or halo-C_1-C_7-alkyl; e.g. C_1-C_7-alkyl, halo-C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkoxy-C_1-C_7-alkyl, phenyloxy- or naphthyloxy-C_1-C_7-alkyl, C_1-C_7-alkanoyloxy-C_1-C_7-alkyl, amino-C_1-C_7-alkyl, such as aminomethyl, C_1-C_7-alkoxy-C_1-C_7-alkylamino-C_1-C_7-alkyl, mono- or di- (C_1-C_7-alkyl-, naphthyl-, phenyl, naphthyl-C_1-C_7-alkyl and/or phenyl-C_1-C_7-alkyl)-amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino-C_1-C_7-alkyl, C_1-C_7-alkyl-O-CO-NH-C_1-C_7-alkyl, C_1-C_7-alkylsulfonylamino-C_1-C_7-alkyl, C_1-C_7-alkyl-NH-CO-NH-C_1-C_7-alkyl, C_1-C_7-alkyl-NH-SO_2-NH-C_1-C_7-alkyl, C_1-C_7-alkoxy, hydroxy-C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, C_1-C_7-alkanoyloxy, halo-C_1-C_7-alkoxy, such as trifluoromethoxy, phenyl- or naphthyl-C_1-C_7-alkanoyloxy, phenyl- or naphthyl-C_1-C_7-alkylaminocarbonyloxy, halo-C_1-C_7-alkylthio, phenyl- or naphthyl-C_1-C_7-alkylthio, mono- or di-(C_1-C_7-alkyl-, naphthyl-C_1-C_7-alkyl-, phenyl-C_1-C_7-alkyl- and/or C_1-C_7-alkoxy-C_1-C_7-alkyl-)amino, C_1-C_7-alkanoylamino, C_1-C_7-alkylsulfonylamino, phenyl- or naphthyl-C_1-C_7-alkanoylamino, phenyl- or naphthyl-C_1-C_7-alkylaminocarbonylamino, carboxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-carbonyl, hydroxy-C_1-C_7-alkoxycarbonyl, C_1-C_7-alkoxy-C_1-C_7-alkoxycarbonyl, amino-C_1-C_7-alkoxycarbonyl, (N-) mono-(C_1-C_7-alkyl)-amino-C_1-C_7-alkoxycarbonyl, C_1-C_7-alkanoylamino-C_1-C_7-alkoxycarbonyl, N- mono- or N,N-di-(C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl and/ or phenyl-C_1-C_7-alkyl)-aminocarbonyl, C_1-C_7-alkylsulfonyl, halo-C_1-C_7-alkylsulfonyl, hydroxy-C_1-C_7-alkylsulfonyl, C_1-C_7-alkoxy-C_1-C_7-alkylsulfonyl, amino-C_1-C_7-alkylsulfonyl, N-mono- or di-(C_1-C_7-alkyl)-amino-C_1-C_7-alkylsulfonyl, C_1-C_7-alkanoylamino-C_1-C_7-alkylsulfonyl, N-C_1-C_7-alkoxy-C_1-C_7-alkylcarbamoyl or N-mono- or N,N-di-(C_1-C_7-alkyl)-aminosulfonyl,

(ii) from C_2-C_7-alkenyl, C_2-C_7-alkynyl, phenyl, naphthyl, mono- or bicyclic heterocyclyl, especially as defined below for mono- or bicyclic heterocyclyl, preferably selected from pyrrolyl, furanyl, thienyl, pyrimidine-2,4-dione-1-, -3- or –5-yl, tetrahydropyranyl and tetrahydrofuranyl, phenyl- or naphthyl- or (mono- or bicyclic heterocyclyl)-C_1-C_7-alkyl or C_1-C_7-alkyloxy wherein mono- or bicyclic heterocyclyl is as defined below, preferably selected from pyrrolyl, furanyl, tetrahydrofuranyl, tetrahydropyranyl and thienyl; tetrahydrofuranyl- or tetrahydropyranyl-C_1-C_7-alkyloxycarbonyl, benzoyl- or naphthoylamino-C_1-C_7-alkyl, (phenyl- or naphthyl- or mono- or bicyclic heterocyclyl)-sulfonylamino-C_1-C_7-alkyl, wherein phenyl or naphthyl or mono- or bicyclic heterocyclyl is unsubstituted or substituted, preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkylsulfonylamino-C_1-C_7-alkyl, halo, hydroxy, phenyl-C_1-C_7-

alkoxy wherein phenyl is preferably unsubstituted or substituted, preferably by C_1-C_7-alkoxy and/or halo, mono- or bicyclic heterocyclyl-C_1-C_7-alkoxy, (mono- or bicyclic heterocyclyl or phenyl or naphthyl)-oxy, naphthyl-C_1-C_7-alkyloxy, benzoyl or naphthoyl or mono- or bicyclic heterocyclylcarbonyl)-oxy, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-aminocarbonyloxy, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-thio, (benzoyl or naphthoyl or mono- or bicyclic heterocyclyl)-thio, nitro, amino, di-((naphthyl or phenyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkyl)-amino, (benzoyl or naphthoyl or mono- or bicyclic heterocyclyl)-amino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-sulfonylamino wherein phenyl or naphthyl is unsubstituted or substituted preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkylsulfonylamino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-aminocarbonylamino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-oxycarbonylamino, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkyloxycarbonylamino, carboxyl, C_1-C_7-alkyl-carbonyl, halo-C_1-C_7-alkylcarbonyl, hydroxy-C_1-C_7-alkylcarbonyl, C_1-C_7-alkoxy-C_1-C_7-alkylcarbonyl, amino-C_1-C_7-alkylcarbonyl, (N-) mono- or (N,N-) di-(C_1-C_7-alkyl)-amino-C_1-C_7-alkylcarbonyl, C_1-C_7-alkanoylamino-C_1-C_7-alkylcarbonyl, halo-C_1-C_7-alkoxycarbonyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-oxy-carbonyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkoxycarbonyl, (N,N-) di-(C_1-C_7-alkyl)-amino-C_1-C_7-alkoxycarbonyl, carbamoyl, N-mono or N,N-di-(naphthyl or phenyl or mono- or bicyclic heterocyclyl)-aminocarbonyl, cyano, C_1-C_7-alkylene which is unsubstituted or substituted by up to four C_1-C_7-alkyl substituents and bound to two adjacent ring atoms of the aryl moiety, sulfenyl, sulfinyl, C_1-C_7-alkylsulfinyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-sulfinyl wherein phenyl or naphthyl is unsubstituted or substituted preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, phenyl- or naphthyl-C_1-C_7-alkylsulfinyl, sulfonyl, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-sulfonyl wherein phenyl or naphthyl is unsubstituted or substituted preferably by one or more, especially one to three, C_1-C_7-alkyl moieties, (phenyl or naphthyl or mono- or bicyclic heterocyclyl)-C_1-C_7-alkylsulfonyl, sulfamoyl and N-mono or N,N-di-(C_1-C_7-alkyl, phenyl-, naphthyl, mono- or bicyclic heterocyclyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl and/or mono- or bicyclic heterocyclyl-C_1-C_7-alkyl)-aminosulfonyl;

where any phenyl or naphthyl or mono- or bicyclic heterocyclyl - which mono- or bicyclic heterocyclyl is preferably as defined for mono- or bicyclic heterocyclyl, more preferably is selected from pyrrolyl, furanyl, tetrahydrofuranyl, tetrahydropyranyl and thienyl - mentioned

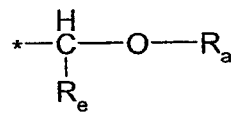
as substituent of or as part of a substituent of mono- or bicyclic heterocyclyl, phenyl or naphthyl R^1 under (i) or (ii) is unsubstituted or substituted by one or more, preferably up to three, moieties independently selected from the group consisting of C_1-C_7-alkyl, C_1-C_7-alkenyl, C_1-C_7-alkynyl, halo-C_1-C_7-alkyl, halo, hydroxy, C_1-C_7-alkoxy, phenyloxy, naphthyloxy, phenyl- or naphthyl-C_1-C_7-alkoxy, C_1-C_7-alkanoyloxy, phenyl- or naphthyl-C_1-C_7-alkanoyloxy, amino, mono- or di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl, C_1-C_7-alkanoyl and/or phenyl- or naphthyl-C_1-C_7-alkanoyl)-amino, carboxy, C_1-C_7-alkoxycarbonyl, phenoxycarbonyl, naphthyloxycabonyl, phenyl-C_1-C_7-alkyloxycarbonyl, naphthyl-C_1-C_7-alkoxycarbonyl, carbamoyl, N-mono- or N,N-di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-aminocarbonyl, cyano, sulfo, sulfamoyl, N-mono- or N,N-di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-aminosulfonyl and nitro, or preferably, where preferred substituents are mentioned, by one or more of these mentioned substituents;

R^2 is phenyl, naphthyl or naphthyl-C_1-C_7-alkyl, wherein each phenyl or naphthyl mentioned so far in the definition of R^2 is unsubstituted or substituted as just described for substituted phenyl or naphthyl in the definition of R^1; or is preferably C_3-C_8-cycloalkyl or is C_1-C_7-alkyl that is unsubstituted or substituted by one or more, especially up to three, e.g. one or two, substituents independently selected from the group consisting of C_2-C_7-alkenyl, C_2-C_7-alkinyl, halo, hydroxy, C_1-C_7-alkoxy, halo-C_1-C_7-alkoxy, hydroxy-C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, phenyl- or naphthyloxy, phenyl- or naphthyl-C_1-C_7-alkyloxy, C_1-C_7-alkanoyloxy, (C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, phenyl and/or phenyl-C_1-C_7-alkyl)-aminocarbonyloxy, benzoyl- or naphthoyloxy, C_1-C_7-alkylthio, halo-C_1-C_7-alkthio, such as trifluoromethylthio, hydroxy-C_1-C_7-alkylthio, C_1-C_7-alkoxy-C_1-C_7-alkylthio, phenyl- or naphthylthio, phenyl- or naphthyl-C_1-C_7-alkylthio, nitro, amino, mono- or di-(C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl and/or C_1-C_7-alkoxy-C_1-C_7-alkyl)-amino, C_1-C_7-alkanoylamino, benzoyl- or naphthoylamino, phenyl- or naphthyl-C_1-C_7-alkylcarbonylamino, C_1-C_7-alkylsulfonylamino, phenyl- or naphthylsulfonylamino wherein phenyl or naphthyl is unsubstituted or substituted by one or more, especially one to three, C_1-C_7-alkyl moieties, phenyl- or naphthyl-C_1-C_7-alkylsulfonylamino, carboxyl, C_1-C_7-alkyl-carbonyl, C_1-C_7-alkoxy-carbonyl, phenyl- or naphthyloxycarbonyl, phenyl- or naphthyl-C_1-C_7-alkoxycarbonyl, carbamoyl, N- mono- or N,N-di-(C_1-C_7-alkyl)-aminocarbonyl, N-mono- or N,N-di-(naphthyl- or phenyl-C_1-C_7-alkyl)-aminocarbonyl, cyano, sulfenyl, sulfonyl, C_1-C_7-alkylsulfinyl, phenyl- or naphthylsulfinyl

wherein phenyl or naphthyl is unsubstituted or substituted by one or more, especially one to three, C_1-C_7-alkyl moieties, phenyl- or naphthyl-C_1-C_7-alkylsulfinyl, sulfonyl, C_1-C_7-alkylsulfonyl, phenyl- or naphthylsulfonyl wherein phenyl or naphthyl is unsubstituted or substituted by one or more, especially one to three, C_1-C_7-alkyl moieties, phenyl- or naphthyl-C_1-C_7-alkylsulfonyl, sulfamoyl, N-mono or N,N-di-(C_1-C_7-alkyl, phenyl-, naphthyl, phenyl-C_1-C_7-alkyl or naphthyl-C_1-C_7-alkyl)-aminosulfonyl, N-mono-, N'-mono-, N,N-di- or N,N,N'-tri-(C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, phenyl and/or phenyl-C_1-C_7-alkyl)-aminocarbonylamino or -aminocarbonyloxy and N-mono-, N'-mono-, N,N-di- or N,N,N'-tri-(C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl and/or C_1-C_7-alkoxy-C_1-C_7-alkyl) aminosulfonylamino; or is C_3-C_{10}-cycloalkyl or C_3-C_{10}-cycloalkyl-C_1-C_7-alkyl;

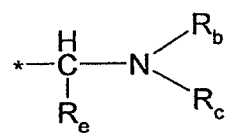
R^3 is a moiety selected from the group of moieties of the formulae

(a)

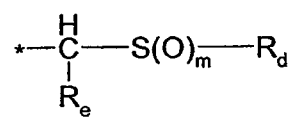


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(b)

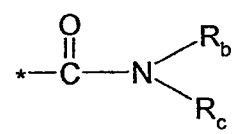


(c)



and

(f)



and

where in any of the moieties of the formulae given above under (a), (b), (c) and (f) the asterisk (*) shows the bond binding the respective moiety R^3 to the rest of the molecule in formula I,

R_a is acyl selected from C_1-C_7-alkanoyl, unsubstituted or mono-, di- or tri-(halo, C_1-C_7-alkoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyl and/or C_1-C_7-alkyl)-substituted) phenyl-C_1-C_7-alkanoyl, C_3-C_8-cycloalkylcarbonyl or C_3-C_8-cycloalkyl-C_1-C_7-alkyl-carbonyl, (tetrahydrofuranyl or tetrahydropyranyl)-carbonyl or (tetrahydrofuranyl or tetrahydropyranyl)-

C_1-C_7-alkyl-carbonyl, N-mono- or N,N-di-(C_1-C_7-alkyl)-aminocarbonyl, N-[phenyl or phenyl-C_1-C_7-alkyl]-aminocarbonyl, N-[C_3-C_8-cycloalkyl or C_3-C_8-cycloalkyl-C_1-C_7-alkyl]-aminocarbonyl, C_1-C_7-alkylaminocarbonyl, N-(phenyl-C_1-C_7-alkyl)(C_1-C_7-alkyl)-aminocarbonyl, N-(phenyl-C_1-C_7-alkyl)(C_3-C_8-cycloalkyl-C_1-C_7-alkyl)-aminocarbonyl, N-(C_1-C_7-alkyl)(C_3-C_8-cycloalkyl-C_1-C_7-alkyl)-aminocarbonyl, N-(phenyl-C_1-C_7-alkyl)(C_3-C_8-cycloalkyl)-aminocarbonyl, N-(heterocyclyl-C_1-C_7-alkyl)(C_3-C_8-cycloalkyl)-aminocarbonyl, N-(heterocyclyl)(C_3-C_8-cycloalkyl)-aminocarbonyl; or is hydrogen;

R_b is C_1-C_7-alkyl or – in each case unsubstituted or substituted - phenyl, naphthyl, phenyl-C_1-C_7-alkyl or naphthyl-C_1-C_7-alkyl wherein in the case of a substituted moiety the substituents are one or more, especially up to three, substituents independently selected from the group consisting of C_1-C_7-alkyl, C_2-C_7-alkenyl, C_2-C_7-alkinyl, hydroxy-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, such as trifluoromethyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, amino-C_1-C_7-alkyl, C_1-C_7-alkoxy, hydroxy-C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, C_1-C_7-alkanoyloxy, amino, mono- or di-(C_1-C_7-alkyl)-amino, C_1-C_7-alkanoylamino, C_1-C_7-alkylsulfonylamino, C_1-C_7-alkoxy-carbonyl, carboxy-C_1-C_7-alkyl, halo, hydroxy, halo-C_1-C_7-alkoxy, halo-C_1-C_7-alkylthio, nitro, carboxyl, C_1-C_7-alkyl-carbonyl, halo-C_1-C_7-alkylcarbonyl, hydroxy-C_1-C_7-alkylcarbonyl, C_1-C_7-alkoxy-C_1-C_7-alkylcarbonyl, halo-C_1-C_7-alkoxycarbonyl, carbamoyl, cyano, C_1-C_7-alkylsulfinyl, sulfonyl, C_1-C_7-alkylsulfonyl, halo-C_1-C_7-alkylsulfonyl, hydroxy-C_1-C_7-alkylsulfonyl, C_1-C_7-alkoxy-C_1-C_7-alkylsulfonyl, sulfamoyl and N-mono or N,N-di-(C_1-C_7-alkyl) -aminosulfonyl; or is acyl as just defined under R_a or in particular

(a) unsubstituted or substituted mono- or bicyclic aryl-carbonyl, wherein the aryl moiety is preferably selected from phenyl, indanyl, indenyl, 1,2,3,4-tetrahydronaphthyl or naphthyl, which is unsubstituted, mono- or di-substituted by C_1-C_7-alkyl, -O-C_1-C_7-alkyl, such as OMe, halo-C_1-C_7-alkyl, halo, such as Cl, -O-C_1-C_7-alkylene-O-alkyl, such as O-$C_3H_6OCH_3$, hydroxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano, unsubstituted or substituted, preferably unsubstituted, heterocyclyl or unsubstituted or substituted, preferably unsubstituted, heterocyclyl-C_1-C_4-alkyl, such as heterocyclyl-CH_2, whereby the heterocyclyl moiety in each case is preferably monocyclic 5- or 6-membered heterocyclyl, preferably containing an N and/or O atom, such as tetrahydrofuranyl or tetrahydropyranyl, piperidinyl, pyrrolidinyl, piperazinyl or morpholinyl;

(b) unsubstituted or substituted mono- or bicyclic heterocyclylcarbonyl, wherein the heterocyclyl moiety is preferably selected from 5 to 11 membered ring systems which may be saturated, partially saturated or aromatic, and having preferably 1, 2 or 3 heteroatoms selected from O, N or S, including pyrrolidinyl, oxazolyl, pyrrolidin-2-onyl, pyrrolyl, piperidyl, furanyl, pyrimidyl, pyridyl, pyrazinyl, isoxazolyl, pyrrolidin-2-onyl, tetrahydrofuranyl, or tetrahydropyranyl; indolyl, 2,3-dihydro-benzo[1,4]dioxinyl, chromanyl, 2H-chromenyl, 3,4-dihydro-1H-quinolin-2-onyl, benzo[d]isoxazolyl, 4,5,6,7-tetrahydro-benzo[d]isoxazolyl, 3a,4,5,6,7,7a-hexahydro-benzo[d]isoxazolyl, 1,4,5,6,-tetrahydro-cyclopentapyrazolyl, 3,4-dihydro-2H-benzo[b][1,4]dioxepinyl, benzofuranyl, 4H-benzo[1,4]oxazin-3-onyl, benzooxazolyl, benzo[1,2,5]oxadiazolyl, benzimidazolyl or 3,4-dihydro-2H-benzo[1,4]oxazinyl, whereby the heterocyclyl moiety is unsubstituted or is mono-substituted with -C_1-C_7-alkyl, such as methyl, halo, hydroxy, C_1-C_7-alkanoyl, unsubstituted or substituted, preferably unsubstituted, phenyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyl, unsubstituted or substituted, preferably unsubstituted, C_3-C_8-cycloalkyl, such as cyclopropyl, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano, more preferably phenyl, -C_1-C_7-alkyl or C_3-C_8-cycloalkyl;

(c) unsubstituted or substituted mono- or bicyclic cycloalkylcarbonyl wherein the cycloalkyl moiety is preferably selected from C_3, C_4, C_5, C_6 and C_7-cycloalkyl which may be unsubstituted or mono-substituted with O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, unsubstituted or substituted phenyl, naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, carboxyl, and cyano;

(d) unsubstituted or substituted alkylcarbonyl wherein the alkyl moiety is preferably selected from branched or straight chain C_1-C_7-alkyl such as isopropyl, isobutyl, sec-butyl or tert-butyl, isopentyl, 1-ethylpropyl, 2,2-dimethyl-propyl and 1,2-dimethyl-propyl, methyl, ethyl or n-propyl, whereby the alkyl moiety is unsubstituted or preferably substituted with O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, unsubstituted or substituted phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, aminocarbonyl, N-mono- or N,N-di-substituted aminocarbonyl, such as CONHMe, carboxyl, C_1-C_7-alkyloxycarbonyl, such as COOMe, and cyano;

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(e) unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkylcarbonyl, such as aryl-CH_2-, aryl-CH_2CH_2-, aryl-$CH(CH_3)$-, aryl-$CH_2CH(CH_3)$- or aryl-$C(CH_3)_2$-, wherein the alkyl moiety, in particular when aryl alkyl is aryl-CH_2- or aryl-CH_2CH_2-, may be mono-substituted with O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, carboxyl, and cyano or unsubstituted or substituted, preferably unsubstituted, phenyl, and wherein the aryl moiety is preferably selected from phenyl, indanyl, indenyl, 1,2,3,4-tetrahydronaphthyl or naphthyl, which may be unsubstituted, mono-, di- or tri-substituted with C_1-C_7-alkyl, -O-C_1-C_7-alkyl, such as OMe, halo-C_1-C_7-alkyl, such as CF_3, halo, such as Cl or F, -O-C_1-C_7-alkylene-O-alkyl, such as O-$C_3H_6OCH_3$, hydroxy, unsubstituted or substituted, preferably substituted, phenyl or naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, carboxyl, and cyano;

(f) unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkylcarbonyl, such as heterocyclyl-CH_2-, heterocyclyl-CH_2CH_2- or heterocyclyl-$CH_2C(CH_3)_2$-, wherein the heterocyclyl moiety is preferably selected from 5 to 11 membered ring systems which may be saturated, partially saturated or aromatic, and having preferably 1, 2 or 3 heteroatoms selected from O, N or S, in particular pyrrolidinyl, oxazolyl, pyrimidyl, pyridyl, pyrazinyl, isoxazolyl, pyrrolidin-2-onyl, pyrrolyl, piperidyl, furanyl, tetrahydrofuranyl, or tetrahydropyranyl; 4H-benzo[1,4]oxazin-3-onyl, benzooxazolyl, indolyl, 2,3-dihydro-benzo[1,4]dioxinyl, chromanyl, 2H-chromenyl, 3,4-dihydro-1H-quinolin-2-onyl, benzo[d]isoxazolyl, 4,5,6,7-tetrahydro-benzo[d]isoxazolyl, 3a,4,5,6,7,7a-hexahydro-benzo[d]isoxazolyl, 1,4,5,6,-tetrahydro-cyclopentapyrazolyl, 3,4-dihydro-2H-benzo[b][1,4]dioxepinyl, benzofuranyl, benzo[1,2,5]oxadiazolyl, benzimidazolyl or 3,4-dihydro-2H-benzo[1,4]oxazinyl, whereby the heterocyclyl moiety is unsubstituted or is mono-substituted -C_1-C_7-alkyl, such as methyl, halo, hydroxy, C_1-C_7-alkanoyl, unsubstituted or substituted, preferably unsubstituted, phenyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyl, unsubstituted or substituted, preferably unsubstituted, C_3-C_8-cycloalkyl, such as cyclopropyl, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano;

(g) unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkylcarbonyl, such as cycloalkyl-CH_2-, cycloalkyl-CH_2CH_2- or cycloalkyl-$CH_2C(CH_3)_2$-, whereby the alkyl moiety may be mono-substituted, including on the carbon where the cycloalkyl moiety is attached, with O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and

cyano, and wherein the cycloalkyl moiety is preferably selected from C_3, C_5 and C_6-cycloalkyl, which may be unsubstituted or substituted with O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, unsubstituted or substituted phenyl, naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, –NHCOEt or –$NHCOCHCH_3)_2$, carboxyl, and cyano;

(h) unsubstituted or substituted alkyloxycarbonyl, wherein the alkyl moiety is preferably selected from branched or straight chain C_1-C_7-alkyl such as isopropyl, isobutyl, sec-butyl or tert-butyl, isopentyl, 1-ethylpropyl, 2,2-dimethyl-propyl and 1,2-dimethyl-propyl, methyl, ethyl, n-propyl, n-butyl or n-pentyl, and which may be unsubsttituted or mono-substituted with O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, unsubstituted or substituted phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, aminocarbonyl, N-mono- or N,N-di-substituted aminocarbonyl, such as CONHMe, carboxyl, C_1-C_7-alkyloxycarbonyl, such as COOMe, and cyano;

(i) unsubstituted or substituted mono- or bicyclic aryl-oxycarbonyl, wherein the aryl moiety is preferably selected from phenyl, indanyl, indenyl, 1,2,3,4-tetrahydronaphthyl or naphthyl, which may be unsubstituted, mono- or di-substituted with C_1-C_7-alkyl, -O-C_1-C_7-alkyl, such as OMe, halo-C_1-C_7-alkyl, halo, such as Cl, -O-C_1-C_7-alkylene-O-alkyl, such as O-$C_3H_6OCH_3$, hydroxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano, unsubstituted or substituted, preferably unsubstituted, heterocyclyl or unsubstituted or substituted, preferably unsubstituted, heterocyclyl-C_1-C_4-alkyl, such as heterocyclyl-CH_2, whereby the heterocyclyl moiety in each case is preferably monocyclic 5- or 6-membered heterocyclyl, preferably containing an N and/or O atom, such as tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, pyrrolidinyl, pyrrolidin-2-onyl, piperazinyl or morpholinyl,

(j) unsubstituted or substituted mono- or bicyclic heterocyclyloxycarbonyl, wherein the heterocyclyl moiety is preferably selected from 5 to 7 membered ring systems which may be saturated, partially saturated or aromatic, and having 1, 2 or 3 heteroatoms selected from O, N or S, in particular pyrrolidinyl, oxazolyl, pyrrolidin-2-onyl, pyrrolyl, piperidyl, furanyl, pyrimidyl, pyridyl, pyrazinyl, isoxazolyl, pyrrolidin-2-onyl, tetrahydrofuranyl, or tetrahydropyranyl, wherein the heterocyclyl moiety is unsubstituted or mono-substituted with -C_1-C_7-alkyl, such as methyl, halo, hydroxy, C_1-C_7-alkanoyl, unsubstituted or substituted,

preferably unsubstituted, phenyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyl, unsubstituted or substituted, preferably unsubstituted, C_3-C_8-cycloalkyl, such as cyclopropyl, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano;

(k) unsubstituted or substituted mono- or bicyclic cycloalkyloxycarbonyl wherein the cycloalkyl moiety is preferably selected from C_3, C_4, C_5, C_6 and C_7-cycloalkyl which may be unsubstituted or substituted with O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, unsubstituted or substituted phenyl, naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, carboxyl, and cyano;

(l) unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyloxycarbonyl, such as aryl-CH_2-, aryl-CH_2CH_2-, aryl-$CH(CH_3)$-, aryl-$CH_2CH(CH_3)$- or aryl-$CH(CH_2CH_3)$-, wherein the aryl moiety is preferably selected from phenyl, indanyl, indenyl, 1,2,3,4-tetrahydronaphthyl or naphthyl, which may be unsubstituted or mono-substituted with C_1-C_7-alkyl, -O-C_1-C_7-alkyl, such as OMe, halo-C_1-C_7-alkyl, such as CF_3, halo, such as Cl or F, -O-C_1-C_7-alkylene-O-alkyl, such as O-$C_3H_6OCH_3$, hydroxy, unsubstituted or substituted, preferably substituted, phenyl or naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, carboxyl, and cyano;

(m) unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkyloxycarbonyl, such as heterocyclyl-CH_2-, heterocyclyl-CH_2CH_2- or heterocyclyl-$CH_2CH(CH_3)$-, wherein the cycloalkyl moiety is preferably selected from 5 to 7 membered ring systems which may be saturated, partially saturated or aromatic, and having 1, 2 or 3, heteroatoms selected from O, N or S, such as pyrrolidinyl, oxazolyl, pyrimidyl, pyridyl, pyrazinyl, isoxazolyl, pyrrolidin-2-onyl, pyrrolyl, piperidyl, furanyl, 1,3-dioxane, tetrahydrofuranyl, or tetrahydropyranyl; whereby the heterocyclyl moiety may be unsubstituted or substituted with -C_1-C_7-alkyl, such as methyl, halo, hydroxy, C_1-C_7-alkanoyl, such as COMe, unsubstituted or substituted, preferably unsubstituted, phenyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyl, unsubstituted or substituted, preferably unsubstituted, C_3-C_8-cycloalkyl, such as cyclopropyl, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano;

(n) unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-oxycarbonyl, such as cycloalkyl-CH_2-, cycloalkyl-CH_2CH_2- or cycloalkyl-$CH_2CH(CH_3)$-, most preferably cycloalkyl-

CH_2-, wherein the cycloalkyl moiety is preferably selected from C_3 and C_5 –cycloalkyl, and may be unsubstituted or substituted with O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, unsubstituted or substituted phenyl, naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, –NHCOEt or –$NHCOCHCH_3)_2$, carboxyl, and cyano,

(o) N-mono- or N,N-di-(unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkyl and/or unsubstituted or substituted alkyl)-aminocarbonyl, whereby

- the alkyl moiety of the unsubstituted or substituted alkyl aminocarbonyl is preferably branched or straight chain C_1-C_7-alkyl such as isopropyl, isobutyl, sec-butyl or tert-butyl, isopentyl, 1-ethylpropyl, 2,2-dimethyl-propyl and 1,2-dimethyl-propyl, methyl, ethyl, n-propyl, n-butyl or n-pentyl, which is unsubstituted or substituted with O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, aminocarbonyl, N-mono- or N,N-di-substituted aminocarbonyl, such as CONHMe, carboxyl, C_1-C_7-alkyloxycarbonyl, such as COOMe, and cyano;

- the aryl moiety of the unsubstituted or substituted aryl aminocarbonyl is preferably phenyl, indanyl, indenyl, 1,2,3,4-tetrahydronaphthyl or naphthyl, which is unsubstituted or mono-substituted with C_1-C_7-alkyl, -O-C_1-C_7-alkyl, such as OMe, halo-C_1-C_7-alkyl, halo, such as Cl, -O-C_1-C_7-alkylene-O-alkyl, such as O-$C_3H_6OCH_3$, hydroxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano,

- the cycloalkyl moiety moiety of the unsubstituted or substituted cycloalkyl aminocarbonyl is preferably C_3 or C_6-cycloalkyl which may be unsubstituted or substituted with O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, unsubstituted or substituted phenyl, naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, carboxyl, and cyano;

- the aryl alkyl moiety of the unsubstituted or substituted aryl alkyl aminocarbonyl is preferably aryl-CH_2-, aryl-CH_2CH_2-, or aryl-$CH(CH_2CH_3)$-, whereby the alkyl moiety, in particular when aryl alkyl is aryl-CH_2-, may be mono-substituted with O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, carboxyl, and cyano or unsubstituted or substituted, preferably unsubstituted, phenyl, and whereby the aryl moiety is preferably phenyl, indanyl, indenyl, 1,2,3,4-tetrahydronaphthyl or naphthyl which is unsubstituted, mono-, di- or tri-substituted with C_1-C_7-alkyl, -O-C_1-C_7-alkyl, such as OMe, halo-C_1-C_7-alkyl, such as CF_3, halo, such as Cl or F, -O-C_1-C_7-alkylene-O-alkyl, such as O-$C_3H_6OCH_3$, hydroxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, carboxyl, and cyano;
- the heterocyclyl alkyl moiety of the unsubstituted or substituted heterocyclyl alkyl aminocarbonyl is preferably heterocyclyl-CH_2- or heterocyclyl-CH_2CH_2-, whereby the heterocyclyl moiety is preferably are selected from 5 to 7 membered ring systems which may be aromatic or saturated rings, and having 1, 2 or 3, heteroatoms selected from O, N or S, such as pyrrolidinyl, oxazolyl, pyrimidyl, pyridyl, pyrazinyl, isoxazolyl, pyrrolidin-2-onyl, pyrrolyl, piperidyl, furanyl, 1,3-dioxane, tetrahydrofuranyl, or tetrahydropyranyl; which may be unsubstituted or mono-substituted with -C_1-C_7-alkyl, such as methyl, halo, hydroxy, C_1-C_7-alkanoyl, such as COMe, unsubstituted or substituted, preferably unsubstituted, phenyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyl, unsubstituted or substituted, preferably unsubstituted, C_3-C_8-cycloalkyl, such as cyclopropyl, nitro, amino, amino-C_1-C_7-alkyl, carboxyl, and cyano;
- the cycloalkyl alkyl moiety of the unsubstituted or substituted cycloalkyl alkyl aminocarbonyl is preferably cycloalkyl-CH_2-, whereby the cycloalkyl moiety is preferably selected from C_6–cycloalkyl which may by unsubstituted or mono-substituted O-C_1-C_4-alkyl, such as OMe, halo, hydroxy, unsubstituted or substituted phenyl, naphthyl, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyloxy, unsubstituted or substituted, preferably unsubstituted, phenyl- or naphthyl-C_1-C_7-alkyloxy, nitro, amino, amino-C_1-C_7-alkyl, C_1-C_7-alkanoylamino, such as –NHCOMe, –NHCOEt or –$NHCOCHCH_3)_2$, carboxyl, and cyano;
When R_b is acyl, R_c is as defined herein, preferably, R_c is hydroxy-C_1-C_7-alkyl, C_1-C_7-alkyloxy-C_1-C_7-alkyl, unsubstituted or substituted C_3-C_8-cycloalkyl-C_1-C_7-alkyl, or preferably hydrogen, unsubstituted or substituted C_3-C_8-cycloalkyl or unsubstituted or substituted C_1-C_7-alkyl, most preferably cyclopropyl or methyl. In particular, when R_b is acyl as defined under (h) to (n), R_c is preferably hydrogen, unsubstituted or substituted C_3-C_8-cycloalkyl or

unsubstituted or substituted C_3-C_8-cycloalkyl C_1-C_7-alkyl or unsubstituted or substituted C_1-C_7-alkyl, most preferably cyclopropyl or methyl or ethyl, in particular, when R_b is acyl as defined under (o), R_c is preferably unsubstituted or substituted C_3-C_8-cycloalkyl most preferably cyclopropyl.

or R_b is selected from unsubstituted mono-, di- or tri-(halo and/or C_1-C_7-alkyl)-substituted (phenyl- or phenyl-C_1-C_7-alkyl)-sulfonyl, C_1-C_7-alkylsulfonyl;

R_c is, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkyloxy-C_1-C_7-alkyl, unsubstituted or substituted C_3-C_8-cycloalkyl-C_1-C_7-alkyl, or preferably hydrogen, unsubstituted or substituted C_3-C_8-cycloalkyl or unsubstituted or substituted C_1-C_7-alkyl;

R_d is unsubstituted or substituted phenyl- or naphthyl-C_1-C_7-alkyl wherein in the case of a substituted moiety the substituents are one or more, especially up to three, substituents independently selected from those mentioned for unsubstituted of substituted phenyl- or naphthyl-C_1-C_7-alkyl under R_b , or is -N(R_b)(R_c);

R_e is C_1-C_7-alkyl or preferably hydrogen; and

m is 2;

each of R^4 and R^5 is selected, independently from the other, from C_1-C_7-alkyl, hydroxy, C_1-C_7-alkyloxy and preferably hydrogen;

and T is carbonyl or preferably methylene;

or a salt thereof.

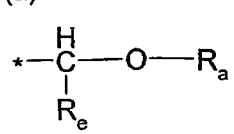
12. A compound of the formula I according to claim 5, wherein

R^1 is phenyl-, indolyl-, quinolyl- or 2,3-dihydro-benzo[1,4]dioxinyl-C_1-C_7-alkanoyl (preferably –carbonyl or –acetyl) wherein the phenyl, indolyl, quinolyl or 2,3-dihydro-benzo[1,4]dioxinyl is substituted by halo, C_1-C_7-alkyloxy-C_1-C_7-alkyloxy, C_1-C_7-alkylene-O-C_1-C_7-alkyl or C_1-C_7-alkyloxy-C_1-C_7-alkyloxy-C_1-C_7-alkyl and may further be substituted by one or more C_1-C_7-alkyl (especially methyl) and/or C_1-C_7-alkyloxy moieties;

R^2 is C_3-C_8-cycloalkyl or preferably C_1-C_7-alkyl ;

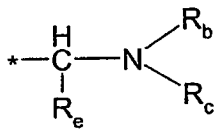
R^3 is a moiety selected from the group of moieties of the formulae

(a)

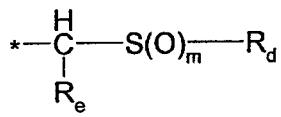


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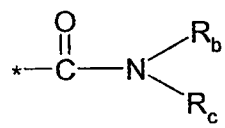
(b)



(c)



(f)



and

where in any of the moieties of the formulae given above under (a), (b), (c) and (f) the asterisk (*) shows the bond binding the respective moiety R^3 to the rest of the molecule in formula I,

wherein

R_a is hydrogen or N-mono- or N,N-di-(C_1-C_7-alkyl, (unsubstituted or halo-substituted) phenyl or naphthyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl C_3-C_8-cycloalkyl-C_1-C_7-alkyl, heterocyclyl-C_1-C_7-alkyl, heterocyclyl and/or C_3-C_8-cycloalkyl)-aminocarbonyl;

each of R_b and R_c is, independently of the other, is selected from hydrogen, C_1-C_7-alkyl, C_3-C_8-cycloalkyl-C_1-C_7-alkyl, C_3-C_8-cycloalkyl, unsubstituted or substituted aryl such as phenyl, naphthyl, naphthyl-C_1-C_7-alkyl, or acyl such as C_3-C_8-cycloalkylcarbonyl, C_3-C_8cycloalkyl-C_1-C_7-alkylcarbonyl, unsubstituted or mono-, di- or tri-(halo, C_1-C_7-alkoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyoxy, C_1-C_7-alkyloxy-C_1-C_7-alkyl and/or C_1-C_7-alkyl)-substituted phenyl- or naphthyl-C_1-C_7-alkanoyl, (tetrahydrofuranyl or tetrahydropyranyl)-carbonyl or (tetrahydrofuranyl or tetrahydropyranyl)-C_1-C_7-alkyl-carbonyl, C_1-C_7-alkylsulfonyl or (unsubstituted or [C_1-C_7-alkyl-, halo-lower alkyl-, halo, C_1-C_7-alkyloxy-, cyano-, C_1-C_7-alkanoyl- and/or C_1-C_7-alkylsulfonyl-]substituted) (phenyl- or naphthyl)-C_1-C_7-alkylsulfonyl,

in particular acyl is selected from

(a) unsubstituted or substituted mono- or bicyclic aryl-carbonyl, wherein the aryl moiety is preferably selected from phenyl, indanyl, or 1,2,3,4-tetrahydronaphthyl which is unsubstituted, mono- or di-substituted by heterocyclyl, heterocyclyl-CH_2, -O-C_1-C_7-alkyl, -O-C_1-C_7-alkylene-O-alkyl and/or halo, whereby the heterocyclyl moiety in each case is preferably monocyclic 5- or 6-membered heterocyclyl, preferably containing an N and/or O

atom, such as tetrahydrofuranyl or tetrahydropyranyl, piperidinyl, pyrrolidinyl, piperazinyl or morpholinyl;

(b) unsubstituted or substituted mono- or bicyclic heterocyclylcarbonyl, wherein the heterocyclyl moiety is preferably selected from 5 to 11 membered ring systems which may be saturated, partially saturated or aromatic, and having preferably 1 or 2 heteroatoms selected from O and/or N, including pyrazinyl, isoxazolyl, pyrrolidin-2-onyl, tetrahydrofuranyl, tetrahydropyranyl, indolyl, 2,3-dihydro-benzo[1,4]dioxinyl, chromanyl, 2H-chromenyl, 3,4-dihydro-1H-quinolin-2-onyl, benzo[d]isoxazolyl, 4,5,6,7-tetrahydro-benzo[d]isoxazolyl, 3a,4,5,6,7,7a-hexahydro-benzo[d]isoxazolyl, 1,4,5,6,-tetrahydro-cyclopentapyrazolyl, or 3,4-dihydro-2H-benzo[b][1,4]dioxepinyl, whereby the heterocyclyl moiety is unsubstituted or is mono-substituted with phenyl, -C_1-C_7-alkyl or C_3-C_8-cycloalkyl;

(c) unsubstituted or substituted mono- or bicyclic cycloalkylcarbonyl wherein the cycloalkyl moiety is preferably selected from C_3, C_4, C_5, C_6 and C_7-cycloalkyl which may be unsubstituted or mono-substituted with O-C_1-C_4-alkyl or hydroxy;

(d) unsubstituted or substituted alkylcarbonyl wherein the alkyl moiety is preferably selected from branched or straight chain C_1-C_7-alkyl such as isobutyl, isopentyl and 2,2-dimethyl-propyl, methyl, ethyl or n-propyl, whereby the alkyl moiety is mono-substituted with -O-C_1-C_7-alkyl, hydroxyl, C_1-C_7-alkanoylamino, unsubstituted or di-substituted phenyloxy, aminocarbonyl, N-mono- or N,N-di-substituted aminocarbonyl and C_1-C_7-alkyloxycarbonyl;

(e) unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkylcarbonyl, such as aryl-CH_2-, aryl-CH_2CH_2-, aryl-$CH(CH_3)$-, aryl-$CH_2CH(CH_3)$- or aryl-$C(CH_3)_2$-, wherein the alkyl moiety, in particular when aryl alkyl is aryl-CH_2- or aryl-CH_2CH_2-, may be mono-substituted with unsubstituted phenyl, C_1-C_7-alkanoylamino, O-C_1-C_4-alkyl or hydroxyl, and wherein the aryl moiety is preferably selected from phenyl or naphthyl, which may be unsubstituted or substituted by -O-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, substituted phenyl, C_1-C_7-alkanoylamino and/or halo;

(f) unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkylcarbonyl, such as heterocyclyl-CH_2-, heterocyclyl-CH_2CH_2- or heterocyclyl-$CH_2C(CH_3)_2$-, wherein the heterocyclyl moiety is preferably selected from 5 to 11 membered ring systems which may be saturated, partially saturated or aromatic, and having preferably 1or 2 heteroatoms selected from O and/or N, in particular pyrrolidinyl, pyrrolidin-2-onyl, pyrrolyl, piperidyl, furanyl, tetrahydrofuranyl, tetrahydropyranyl, 4H-benzo[1,4]oxazin-3-onyl or benzooxazolyl, whereby the heterocyclyl moiety is unsubstituted or is mono-substituted with unsubstituted phenyl, -C_1-C_7-alkyl or C_1-C_7-alkanoyl;

(g) unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkylcarbonyl, such as cycloalkyl-CH_2-, whereby the alkyl moiety may be mono-substituted, including on the carbon where the cycloalkyl moiety is attached, with -C_1-C_4-alkyl or hydroxyl, and wherein the cycloalkyl moiety is preferably selected from C_3, C_5 and C_6-cycloalkyl, which may be unsubstituted or mono-substituted with amino, O-C_1-C_4-alkyl or hydroxy;

(h) unsubstituted or substituted alkyloxycarbonyl, wherein the alkyl moiety is preferably selected from branched or straight chain C_1-C_7-alkyl such as isobutyl, isopentyl and 2,2-dimethyl-propyl, methyl or ethyl, and which may be mono-substituted with by -O-C_1-C_7-alkyl, C_1-C_7-alkanoylamino and N-mono- or N,N-di-substituted aminocarbonyl;

(i) unsubstituted or substituted mono- or bicyclic aryl-oxycarbonyl, wherein the aryl moiety is preferably selected from phenyl or naphthyl, which may be unsubstituted, mono-substituted with heterocyclyl or -O-C_1-C_7-alkyl, whereby the heterocyclyl moiety is monocyclic 5- or 6-membered heterocyclyl, containing an N and/or O atom, such as tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, pyrrolidinyl, pyrrolidin-2-onyl, piperazinyl or morpholinyl;

(j) unsubstituted or substituted mono- or bicyclic heterocyclyloxycarbonyl, wherein the heterocyclyl moiety is preferably selected from 5 to 7 membered ring systems which may be saturated, partially saturated or aromatic, and having 1 or 2 heteroatoms selected from O and/or N, in particular tetrahydrofuranyl or tetrahydropyranyl, wherein the heterocyclyl moiety is unsubstituted;

(k) unsubstituted or substituted mono- or bicyclic cycloalkyloxycarbonyl wherein the cycloalkyl moiety is preferably selected from C_6-cycloalkyl which is unsubstituted;

(l) unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyloxycarbonyl, such as aryl-CH_2-, aryl-CH_2CH_2-, aryl-$CH(CH_3)$-, aryl-$CH_2CH(CH_3)$- or aryl-$CH(CH_2CH_3)$-, wherein the aryl moiety is preferably selected from phenyl which is unsubstituted;

(m) unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkyloxycarbonyl, such as heterocyclyl-CH_2-, heterocyclyl-CH_2CH_2- or heterocyclyl-$CH_2CH(CH_3)$-, wherein the cycloalkyl moiety is preferably selected from 5 to 7 membered ring systems which may be saturated, partially saturated or aromatic, and having 1 or 2 heteroatoms selected from O and/or N, such as pyridyl, piperidyl, isoxazolyl, tetrahydrofuranyl, tetrahydropyranyl or 1,3-dioxane, which is unsubstituted or is mono-substituted with -C_1-C_7-alkyl or C_1-C_7-alkanoyl;

(n) unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-oxycarbonyl, such as cycloalkyl-CH_2-, wherein the cycloalkyl moiety is preferably selected from C_3 and C_5-cycloalkyl, and may be unsubstituted or substituted with C_1-C_7-alkanoylamino,

(o) N-mono- or N,N-di-(unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkyl and/or unsubstituted or substituted alkyl)-aminocarbonyl, whereby

- the alkyl moiety of the unsubstituted or substituted alkyl aminocarbonyl is preferably branched or straight chain C_1-C_7-alkyl such as isopropyl, isobutyl, methyl or ethyl, which is unsubstituted;
- the aryl moiety of the unsubstituted or substituted aryl aminocarbonyl is preferably phenyl or naphthyl, which is unsubstituted,
- the cycloalkyl moiety moiety of the unsubstituted or substituted cycloalkyl aminocarbonyl is preferably C_3 or C_6-cycloalkyl which is unsubstituted;
- the aryl alkyl moiety of the unsubstituted or substituted aryl alkyl aminocarbonyl is preferably aryl-CH_2-, aryl-CH_2CH_2-, or aryl-$CH(CH_2CH_3)$-, whereby the alkyl moiety, in particular when aryl alkyl is aryl-CH_2-, may be mono-substituted with unsubstituted phenyl, and whereby the aryl moiety is preferably phenyl, which is unsubstituted;
- the heterocyclyl alkyl moiety of the unsubstituted or substituted heterocyclyl alkyl aminocarbonyl is preferably heterocyclyl-CH_2- whereby the heterocyclyl moiety is preferably are selected from 5 to 7 membered ring systems which may be aromatic or saturated rings, and having 1 or 2 heteroatoms selected from Oand/or N, such as furanyl or tetrahydropyranyl; which is unsubstituted;
- the cycloalkyl alkyl moiety of the unsubstituted or substituted cycloalkyl alkyl aminocarbonyl is preferably cycloalkyl-CH_2-, whereby the cycloalkyl moiety is preferably selected from C_6–cycloalkyl which is unsubstituted;

with the proviso that if R_c is hydrogen, C_1-C_7-alkyl, phenyl, naphthyl or naphthyl-C_1-C_7-alkyl, then R_b can also be phenyl-C_1-C_7-alkyl;

R_d is unsubstituted or [C_1-C_7-alkyl-, phenyl-, halo-lower alkyl-, halo, oxo-C_1-C_7-alkyl-, C_1-C_7-alkyloxy-, phenyl-C_1-C_7-alkoxy-, halo-C_1-C_7-alkyloxy-, phenoxy-, C_1-C_7-alkanoylamino-, cyano-, C_1-C_7-alkanoyl- and/or C_1-C_7-alkylsulfonyl-]substituted (phenyl- or naphthyl)-C_1-C_7-alkyl;

R_e is hydrogen; and

m is 2;

each of R^4 and R^5 is hydrogen; and

T is carbonyl or preferably methylene;

or a salt thereof.

13. A compound of the formula I according to claim 5, selected from the group of compounds:
N-((3S*,4S*)-4-{[(3-Acetylamino-3-methyl-butyryl)-cyclopropyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide
N-[(3S*,4S*)-4-({Cyclopropyl-[2-(2-oxo-pyrrolidin-1-yl)-acetyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide
N-[(3S*,4S*)-4-({[2-(1-Acetylamino-cyclopentyl)-acetyl]-cyclopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide
N-((3S*,4S*)-4-{[Cyclopropyl-(3,3-dimethyl-butyryl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide
N-[(3S*,4S*)-4-({[2-(1-Acetylamino-cyclohexyl)-acetyl]-cyclopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide
N-((3S*,4S*)-4-{[Cyclopropyl-(3-methyl-3-pyrrol-1-yl-butyryl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide
N-[(3S*,4S*)-4-({Cyclopropyl-[2-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-acetyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide
N-[(3S*,4S*)-4-({Cyclopropyl-[2-(1-isobutyrylamino-cyclopentyl)-acetyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide
N-((3S*,4S*)-4-{[Cyclopropyl-(4-methyl-pentanoyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide
N-[(3S*,4S*)-4-({Cyclopropyl-[2-(2-methyl-benzooxazol-5-yl)-acetyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide
N-((3S*,4S*)-4-{[(3-Cyclohexyl-propionyl)-cyclopropyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide
N-((3S,4S)-4-{[Cyclopropyl-(3-cyclopropyl-propionyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide
N-((3S,4S)-4-{[(3-Cyclopentyl-propionyl)-cyclopropyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide
N-((3S,4S)-4-{[Cyclopropyl-(3,3-diphenyl-propionyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S,4S)-4-({Cyclopropyl-[2-(2,6-dimethyl-phenoxy)-acetyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-((S)-3-phenyl-butyryl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S,4S)-4-({[2-(1-Acetyl-piperidin-4-yl)-acetyl]-cyclopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[((S)-3-Acetylamino-3-phenyl-propionyl)-cyclopropyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[((R)-3-Acetylamino-3-phenyl-propionyl)-cyclopropyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-((R)-3-hydroxy-3-phenyl-propionyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-((S)-3-hydroxy-3-phenyl-propionyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-(3-furan-2-yl-propionyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-(2-furan-2-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-((S)-2-methoxy-2-cyclohexyl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-((S)-2-hydroxy-4-methyl-pentanoyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-{(3S*,4S*)-4-[(Cyclohexanecarbonyl-cyclopropyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

Cycloheptanecarboxylic acid cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

N-((3S,4S)-4-{[(2-Cyclopentyl-acetyl)-cyclopropyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S*,4S*)-4-{[(2-Cyclohexyl-acetyl)-cyclopropyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-{(3S*,4S*)-4-[(Benzoyl-cyclopropyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-({Cyclopropyl-[2-(4-fluoro-phenyl)-acetyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S,4S)-4-({[2-(4-Chloro-phenyl)-acetyl]-cyclopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-({[2-(3-Chloro-phenyl)-acetyl]-cyclopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-({Cyclopropyl-[2-(2-methoxy-phenyl)-acetyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-({Cyclopropyl-[2-(3,5-difluoro-phenyl)-acetyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-({Cyclopropyl-[2-(2,3,5-trifluoro-phenyl)-acetyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-({Cyclopropyl-[2-(3-trifluoromethyl-phenyl)-acetyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-({[2-(3,5-Bis-trifluoromethyl-phenyl)-acetyl]-cyclopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S*,4S*)-4-{[Cyclopropyl-(3-pyrrolidin-1-yl-benzoyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-({Cyclopropyl-[2-(3'-fluoro-biphenyl-3-yl)-acetyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S*,4S*)-4-{[Cyclopropyl-(3-chloro-6-methoxy-1-yl-benzoyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S*,4S*)-4-{[Cyclopropyl-(4-morpholin-4-ylmethyl-benzoyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

1H-Indole-2-carboxylic acid cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

1H-Indole-3-carboxylic acid cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

2,3-Dihydro-benzo[1,4]dioxine-6-carboxylic acid cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

N-((3S*,4S*)-4-{[Cyclopropyl-(2-naphthalen-2-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-(2-phenoxy-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S*,4S*)-4-{[Cyclopropyl-((S)-2-phenyl-propionyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

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N-((3S*,4S*)-4-{[Cyclopropyl-((R)-2-phenyl-propionyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-((S)-2-hydroxy-2-phenyl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-((R)-2-hydroxy-2-phenyl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-((R)-2-methoxy-2-phenyl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-((S)-2-methoxy-2-phenyl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

Tetrahydro-furan-3-carboxylic acid cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

Tetrahydro-furan-2-carboxylic acid cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

(S)-Tetrahydro-pyran-3-carboxylic acid cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

(R)-Tetrahydro-pyran-3-carboxylic acid cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

Tetrahydro-pyran-4-carboxylic acid cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

N-((3S,4S)-4-{[Cyclopropyl-(4-hydroxy-cyclohexanecarbonyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-(cis-4-methoxy-cyclohexanecarbonyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-(trans-4-methoxy-cyclohexanecarbonyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-((S)-2-tetrahydro-furan-2-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-((R)-2-tetrahydro-furan-2-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-((S)-2-tetrahydro-pyran-2-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-((R)-2-tetrahydro-pyran-2-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

(R)-1,2,3,4-Tetrahydro-naphthalene-2-carboxylic acid cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

(S)-1,2,3,4-Tetrahydro-naphthalene-2-carboxylic acid cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

N-((3S*,4S*)-4-{[Cyclopropyl-(2-tetrahydro-pyran-4-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

Chroman-2-carboxylic acid cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

2H-Chromene-3-carboxylic acid cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

(R)-2,3-Dihydro-benzo[1,4]dioxine-2-carboxylic acid cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

(S)-2,3-Dihydro-benzo[1,4]dioxine-2-carboxylic acid cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

2-Oxo-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

4,5,6,7-Tetrahydro-benzo[d]isoxazole-3-carboxylic acid cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

3a,4,5,6,7,7a-Hexahydro-benzo[d]isoxazole-3-carboxylic acid cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

N-((3S,4S)-4-{[(2-Benzo[d]isoxazol-3-yl-acetyl)-cyclopropyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

1,4,5,6-Tetrahydro-cyclopentapyrazole-3-carboxylic acid cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

Isoxazole-3-carboxylic acid cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

5-Methyl-isoxazole-3-carboxylic acid cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

5-Cyclopropyl-isoxazole-3-carboxylic acid cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

5-Phenyl-isoxazole-3-carboxylic acid cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

5-Methyl-pyrazine-2-carboxylic acid cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

Indan-2-carboxylic acid cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

5-Oxo-1-phenyl-pyrrolidine-3-carboxylic acid cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

N-Cyclopropyl-N-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-succinamide

N-Cyclopropyl-N-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-N'-methyl-succinamide

N-Cyclopropyl-N-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-succinamic acid methyl ester

N-((3S,4S)-4-{[Cyclopropyl-(2-piperidin-4-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S,4S)-4-({[2-(4-Amino-cyclohexyl)-acetyl]-cyclopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S,4S)-4-({[2-(4-Amino-cyclohexyl)-acetyl]-cyclopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-(2-methyl-2-phenyl-propionyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[((S)-2-Hydroxy-2-phenyl-acetyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[((S)-2-Methoxy-2-phenyl-acetyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[((S)-2-Hydroxy-4-methyl-pentanoyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[((S)-2-Methoxy-2-cyclohexyl-acetyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[((S)-2-Hydroxy-3-methyl-butyryl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[((S)-2-Hydroxy-3-phenyl-propionyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[((S)-2-Cyclohexyl-2-hydroxy-acetyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

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N-((3S,4S)-4-{[((S)-3-Hydroxy-3-phenyl-propionyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[((R)-3-Hydroxy-3-phenyl-propionyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[(2-Furan-2-yl-acetyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[((S)-2-Methoxy-3-methyl-butyryl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[((S)-2-Methoxy-4-methyl-pentanoyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-{(3S*,4S*)-4-[(Benzoyl-methyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[(2-Cyclohexyl-acetyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-Isopropyl-4-methoxy-N-[(3S*,4S*)-4-({[2-(3-methoxy-phenyl)-acetyl]-methyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-3-(3-methoxy-propoxy)-benzamide

Indan-2-carboxylic acid [(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-amide

(R)-1,2,3,4-Tetrahydro-naphthalene-2-carboxylic acid [(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-amide

(S)-1,2,3,4-Tetrahydro-naphthalene-2-carboxylic acid [(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-amide

Tetrahydro-pyran-4-carboxylic acid [(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-amide

N-[(3S,4S)-4-({[2-(1-Hydroxy-cyclohexyl)-acetyl]-methyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-Isopropyl-4-methoxy-N-[(3S,4S)-4-({[2-(4-methoxy-cyclohexyl)-acetyl]-methyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-3-(3-methoxy-propoxy)-benzamide

N-Isopropyl-4-methoxy-N-[(3S,4S)-4-({[2-(4-methoxy-cyclohexyl)-acetyl]-methyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-3-(3-methoxy-propoxy)-benzamide

3,4-Dihydro-2H-benzo[b][1,4]dioxepine-2-carboxylic acid [(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-amide

N-Isopropyl-4-methoxy-N-((3S,4S)-4-{[(cis-4-methoxy-cyclohexanecarbonyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-3-(3-methoxy-propoxy)-benzamide

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N-Isopropyl-4-methoxy-N-((3S,4S)-4-{[(trans-4-methoxy-cyclohexanecarbonyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-3-(3-methoxy-propoxy)-benzamide

N-Isopropyl-4-methoxy-3-(3-methoxy-propoxy)-N-[(3S,4S)-4-(phenylacetylamino-methyl)-pyrrolidin-3-ylmethyl]-benzamide

Indan-2-carboxylic acid [(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

N-{(3S,4S)-4-[((S)-2-Cyclohexyl-2-methoxy-acetylamino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-Isopropyl-4-methoxy-N-{(3S,4S)-4-[((R)-2-methoxy-2-phenyl-acetylamino)-methyl]-pyrrolidin-3-ylmethyl}-3-(3-methoxy-propoxy)-benzamide

N-Isopropyl-4-methoxy-N-{(3S,4S)-4-[((S)-2-methoxy-2-phenyl-acetylamino)-methyl]-pyrrolidin-3-ylmethyl}-3-(3-methoxy-propoxy)-benzamide

N-{(3S,4S)-4-[((R)-2-Cyclohexyl-2-methoxy-acetylamino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-{(3S,4S)-4-[(Ethyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Ethyl-(2-tetrahydro-pyran-4-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-{(3S*,4S*)-4-[(Cyclobutyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S*,4S*)-4-{[Cyclobutyl-(2-tetrahydro-pyran-4-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-Isopropyl-N-{(3S*,4S*)-4-[(isopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-Isopropyl-N-((3S*,4S*)-4-{[isopropyl-(2-tetrahydro-pyran-4-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-{(3S*,4S*)-4-[(Cyclopropanecarbonyl-isobutyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-{(3S*,4S*)-4-[(Cyclobutanecarbonyl-isobutyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S*,4S*)-4-{[Isobutyl-(2-tetrahydro-pyran-4-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-{(3S*,4S*)-4-[(Isobutyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-{(3S*,4S*)-4-[(Cyclopropylmethyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-((3S*,4S*)-4-{[Cyclopropylmethyl-(2-tetrahydro-pyran-4-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

1-(3-Methoxy-propyl)-3-methyl-1H-indole-6-carboxylic acid isopropyl-{(3S,4S)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-amide

1-(3-Methoxy-propyl)-3-methyl-1H-indole-6-carboxylic acid ((3S,4S)-4-{[(2-cyclohexyl-acetyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-isopropyl-amide

N-{(3S,4S)-4-[(Cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-4-ethyl-N-isopropyl-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[(2-Cyclohexyl-acetyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-4-ethyl-N-isopropyl-3-(3-methoxy-propoxy)-benzamide

4-Ethyl-N-isopropyl-3-(3-methoxy-propoxy)-N-((3S,4S)-4-{[methyl-(2-tetrahydro-pyran-4-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-benzamide

Tetrahydro-pyran-4-carboxylic acid [(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-amide

N-((3S,4S)-4-{[Cyclopropyl-(2-tetrahydro-pyran-4-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-4-ethyl-N-isopropyl-3-(3-methoxy-propoxy)-benzamide

Tetrahydro-pyran-4-carboxylic acid cyclopropyl-[(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

N-((3S,4S)-4-{[(3-Acetylamino-3-methyl-butyryl)-cyclopropyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-4-ethyl-N-isopropyl-3-(3-methoxy-propoxy)-benzamide

4-Ethyl-N-((3S,4S)-4-{[((S)-2-hydroxy-2-phenyl-acetyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-benzamide

N-[(3S,4S)-4-({[2-(1-Acetyl-piperidin-4-yl)-acetyl]-cyclopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-4-ethyl-N-isopropyl-3-(3-methoxy-propoxy)-benzamide

N-[(3S,4S)-4-({[2-(1-Acetyl-piperidin-4-yl)-acetyl]-methyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-4-ethyl-N-isopropyl-3-(3-methoxy-propoxy)-benzamide

4-Ethyl-N-((3S,4S)-4-{[((S)-2-hydroxy-4-methyl-pentanoyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-benzamide

4-Ethyl-N-((3S,4S)-4-{[((S)-2-hydroxy-3-methyl-butyryl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-benzamide

Indan-2-carboxylic acid [(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

4-Ethyl-N-isopropyl-3-(3-methoxy-propoxy)-N-{(3S,4S)-4-[(2-methyl-2-phenyl-propionylamino)-methyl]-pyrrolidin-3-ylmethyl}-benzamide

4-Ethyl-N-isopropyl-N-{(3S,4S)-4-[((R)-2-methoxy-2-phenyl-acetylamino)-methyl]-pyrrolidin-3-ylmethyl}-3-(3-methoxy-propoxy)-benzamide

4-Ethyl-N-[(3S,4S)-4-({[2-(1-hydroxy-cyclohexyl)-acetyl]-methyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-3-(3-methoxy-propoxy)-benzamide

N-[(3S,4S)-4-({[2-(4-Amino-cyclohexyl)-acetyl]-methyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-4-ethyl-N-isopropyl-3-(3-methoxy-propoxy)-benzamide

N-[(3S,4S)-4-({[2-(4-Amino-cyclohexyl)-acetyl]-methyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-4-ethyl-N-isopropyl-3-(3-methoxy-propoxy)-benzamide

5-Methyl-pyrazine-2-carboxylic acid [(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-amide

(S)-2,3-Dihydro-benzo[1,4]dioxine-2-carboxylic acid [(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-amide

(R)-2-Oxo-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid [(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-amide

(S)-2-Oxo-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid [(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-amide

N-Cyclopropyl-N-[(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-N'-methyl-succinamide

5-Methyl-pyrazine-2-carboxylic acid cyclopropyl-[(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

Isoxazole-3-carboxylic acid cyclopropyl-[(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

N-[(3S,4S)-4-({[2-(4-Amino-cyclohexyl)-acetyl]-cyclopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-4-ethyl-N-isopropyl-3-(3-methoxy-propoxy)-benzamide

N-[(3S,4S)-4-({[2-(4-Amino-cyclohexyl)-acetyl]-cyclopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-4-ethyl-N-isopropyl-3-(3-methoxy-propoxy)-benzamide

(R)-Tetrahydro-furan-3-carboxylic acid cyclopropyl-[(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

(S)-Tetrahydro-furan-3-carboxylic acid cyclopropyl-[(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

(R)-Tetrahydro-pyran-3-carboxylic acid cyclopropyl-[(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

(S)-Tetrahydro-pyran-3-carboxylic acid cyclopropyl-[(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

N-((3S,4S)-4-{[Cyclopropyl-(cis-4-hydroxy-cyclohexanecarbonyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-4-ethyl-N-isopropyl-3-(3-methoxy-propoxy)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-(trans-4-hydroxy-cyclohexanecarbonyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-4-ethyl-N-isopropyl-3-(3-methoxy-propoxy)-benzamide

(S)-Tetrahydro-pyran-3-carboxylic acid [(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-amide

(R)-Tetrahydro-pyran-3-carboxylic acid [(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-amide

N-Isopropyl-3-(3-methoxy-propoxy)-4-methyl-N-{(3S,4S)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-benzamide

Tetrahydro-pyran-4-carboxylic acid [(3S,4S)-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-amide

N-Isopropyl-3-(3-methoxy-propoxy)-4-methyl-N-((3S,4S)-4-{[methyl-(2-tetrahydro-pyran-4-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-((S)-2-methoxy-2-phenyl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

(S)-2,3-Dihydro-benzo[1,4]dioxine-2-carboxylic acid cyclopropyl-[(3S,4S)-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

N-((3S,4S)-4-{[((S)-2-Methoxy-2-phenyl-acetyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

(S)-2,3-Dihydro-benzo[1,4]dioxine-2-carboxylic acid [(3S,4S)-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-amide

N-((3S,4S)-4-{[(3-Acetylamino-3-methyl-butyryl)-cyclopropyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-((3S,4S)-4-{[((S)-2-Hydroxy-2-phenyl-acetyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

Tetrahydro-pyran-4-carboxylic acid cyclopropyl-[(3S,4S)-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

N-Isopropyl-3-(3-methoxy-propoxy)-4-methyl-N-[(3S,4S)-4-({methyl-[2-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-acetyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-benzamide

N-[(3S,4S)-4-({Cyclopropyl-[2-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)-acetyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-((3S,4S)-4-{[Cyclopropyl-(2-tetrahydro-pyran-4-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-((3S,4S)-4-{[((S)-2-Cyclohexyl-2-methoxy-acetyl)-cyclopropyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-((3S,4S)-4-{[((S)-2-Cyclohexyl-2-methoxy-acetyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-((3S,4S)-4-{[((S)-2-Hydroxy-3-methyl-butyryl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-[(3S,4S)-4-({[2-(1-Acetyl-piperidin-4-yl)-acetyl]-cyclopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-((3S,4S)-4-{[((S)-2-Hydroxy-4-methyl-pentanoyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-((3S,4S)-4-{[(cis-4-Hydroxy-cyclohexanecarbonyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-((3S,4S)-4-{[((R)-3-Hydroxy-3-phenyl-propionyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-((3S,4S)-4-{[((S)-3-Hydroxy-3-phenyl-propionyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-[(3S,4S)-4-({[2-(1-Acetyl-piperidin-4-yl)-acetyl]-methyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-((3S,4S)-4-{[Cyclopropyl-(cis-4-hydroxy-cyclohexanecarbonyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-((3S,4S)-4-{[((S)-2-Hydroxy-3-phenyl-propionyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-((3S,4S)-4-{[(2-Furan-2-yl-acetyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-((3S,4S)-4-{[Cyclopropyl-((S)-2-hydroxy-4-methyl-pentanoyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

Indan-2-carboxylic acid [(3S,4S)-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

N-Isopropyl-3-(3-methoxy-propoxy)-4-methyl-N-{(3S,4S)-4-[(2-methyl-2-phenyl-propionylamino)-methyl]-pyrrolidin-3-ylmethyl}-benzamide

N-Isopropyl-3-(3-methoxy-propoxy)-4-methyl-N-{(3S,4S)-4-[(2-tetrahydro-pyran-4-yl-acetylamino)-methyl]-pyrrolidin-3-ylmethyl}-benzamide

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(S)-2,3-Dihydro-benzo[1,4]dioxine-2-carboxylic acid [(3S,4S)-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

N-Isopropyl-3-(3-methoxy-propoxy)-4-methyl-N-((3S,4S)-4-{[methyl-((R)-2-tetrahydro-pyran-2-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-benzamide

N-Isopropyl-3-(3-methoxy-propoxy)-4-methyl-N-((3S,4S)-4-{[methyl-((S)-2-tetrahydro-pyran-2-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-benzamide

N-((3S,4S)-4-{[Cyclopropyl-((R)-2-tetrahydro-furan-2-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-((3S,4S)-4-{[Cyclopropyl-((S)-2-tetrahydro-furan-2-yl-acetyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-N-isopropyl-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-Isopropyl-N-((3S,4S)-4-{[(cis-4-methoxy-cyclohexanecarbonyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-Isopropyl-N-((3S,4S)-4-{[(trans-4-methoxy-cyclohexanecarbonyl)-methyl-amino]-methyl}-pyrrolidin-3-ylmethyl)-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-Isopropyl-N-((3S,4S)-4-{[(cis-4-methoxy-cyclohexanecarbonyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-3-(3-methoxy-propoxy)-4-methyl-benzamide

N-Isopropyl-N-((3S,4S)-4-{[(trans-4-methoxy-cyclohexanecarbonyl)-amino]-methyl}-pyrrolidin-3-ylmethyl)-3-(3-methoxy-propoxy)-4-methyl-benzamide

1-(3-Methoxy-propyl)-1H-indole-6-carboxylic acid isopropyl-{(3S,4S)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-amide

N-Cyclopropyl-N-{(3S,4S)-4-[(cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-4-methoxy-3-(3-methoxy-propoxy)-benzamide

Cyclopropyl-[(3S,4S)-4-({cyclopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid benzyl ester

Cyclopropyl-[(3S,4S)-4-({cyclopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid isobutyl ester

Cyclopropyl-[(3S,4S)-4-({cyclopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid tetrahydro-pyran-4-yl ester

Cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid benzyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid benzyl ester

Cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid isobutyl ester

Cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid pyridin-4-ylmethyl ester

Cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 1-methyl-piperidin-4-ylmethyl ester

Cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 2-methoxy-ethyl ester

Cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid tetrahydro-pyran-4-ylmethyl ester

Cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 2,2-dimethyl-propyl ester

Cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 1-methyl-cyclopropylmethyl ester

Cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 2-acetylamino-2-methyl-propyl ester

Cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid phenyl ester

Cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 2-methyl-2-methylcarbamoyl-propyl ester

Cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 1-acetylamino-cyclopentylmethyl ester

Cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 1-acetyl-piperidin-4-ylmethyl ester

Cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 5-methyl-isoxazol-3-ylmethyl ester

Cyclopropyl-[(3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid naphthalen-1-yl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid cyclopropylmethyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid isobutyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 4-methoxy phenyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid cyclohexyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid naphthalen-2-yl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid tetrahydro-pyran-4-yl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 5-methyl-[1,3]dioxan-5-ylmethyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 3-(2-oxo-pyrrolidin-1-yl)-phenyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 3-morpholin-4-yl-phenyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid (R)-1-(tetrahydro-furan-2-yl)methyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid (R)-1-phenyl-propyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid (R)-1-phenyl-ethyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid phenyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 2-methoxy phenyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 3-methoxy-3-methyl-butyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid (R)-(tetrahydro-furan-3-yl) ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid (S)-(tetrahydro-furan-3-yl) ester

[(3S,4S)-4-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-carbamic acid 3-methoxy-3-methyl-butyl ester

[(3S,4S)-4-({Isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-carbamic acid tetrahydro-pyran-4-yl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid tetrahydro-pyran-4-yl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid (S)-(tetrahydro-furan-3-yl) ester

[(3S,4S)-4-({Isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-carbamic acid tetrahydro-pyran-4-yl ester

[(3S,4S)-4-({Isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-carbamic acid (S)-(tetrahydro-furan-3-yl) ester

[(3S,4S)-4-({Isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-carbamic acid 3-methoxy-3-methyl-butyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 3-methoxy-3-methyl-butyl ester

[(3S,4S)-4-({Isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-carbamic acid 4-methoxy phenyl ester

[(3S,4S)-4-({Isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-carbamic acid (R)-1-(tetrahydro-furan-2-yl)methyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 4-methoxy phenyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid (R)-1-(tetrahydro-furan-2-yl)methyl ester

[(3S,4S)-4-({Isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-carbamic acid 5-methyl-[1,3]dioxan-5-ylmethyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 5-methyl-isoxazol-3-ylmethyl ester

[(3S,4S)-4-({Isopropyl-[3-(3-methoxy-propoxy)-4-methyl-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-carbamic acid 5-methyl-isoxazol-3-ylmethyl ester

Cyclopropyl-[(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid benzyl ester

Cyclopropyl-[(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid tetrahydro-pyran-4-yl ester

Cyclopropyl-[(3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid 4-methoxy phenyl ester

[(3S,4S)-4-({[4-Ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-carbamic acid tetrahydro-pyran-4-yl ester

[(3S,4S)-4-({[4-Ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-carbamic acid (R)-1-(tetrahydro-furan-2-yl)methyl ester

[(3S,4S)-4-({[4-Ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-carbamic acid (S)-(tetrahydro-furan-3-yl) ester

[(3S,4S)-4-({[4-Ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-carbamic acid 5-methyl-[1,3]dioxan-5-ylmethyl ester

[(3S,4S)-4-({[4-Ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl]-methyl-carbamic acid 3-methoxy-3-methyl-butyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[1-(3-methoxy-propyl)-3-methyl-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid benzyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[1-(3-methoxy-propyl)-3-methyl-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid isobutyl ester

Cyclopropyl-[(3S,4S)-4-({isopropyl-[1-(3-methoxy-propyl)-3-methyl-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-carbamic acid tetrahydro-pyran-4-yl ester

Benzyl-methyl-carbamic acid (3S*,4S*)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl ester

Diisobutyl-carbamic acid (3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl ester

Benzyl-cyclopropyl-carbamic acid (3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl ester

Isobutyl-methyl-carbamic acid (3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl ester

Cyclopropyl-(tetrahydro-pyran-4-ylmethyl)-carbamic acid (3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl ester

Cyclopropyl-(tetrahydro-pyran-4-yl)-carbamic acid (3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl ester

Cyclohexylmethyl-methyl-carbamic acid (3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl ester

Benzyl-cyclopropyl-carbamic acid (3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl ester

Cyclopropyl-(tetrahydro-pyran-4-ylmethyl)-carbamic acid (3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl ester

Cyclopropyl-(tetrahydro-pyran-3-ylmethyl)-carbamic acid (3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl ester

Cyclopropyl-(tetrahydro-pyran-4-yl)-carbamic acid (3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl ester

Cyclopropyl-(tetrahydro-pyran-2-ylmethyl)-carbamic acid (3S,4S)-4-({[4-ethyl-3-(3-methoxy-propoxy)-benzoyl]-isopropyl-amino}-methyl)-pyrrolidin-3-ylmethyl ester

Cyclopropyl-(tetrahydro-pyran-4-yl)-carbamic acid (3S,4S)-4-({isopropyl-[1-(3-methoxy-propyl)-3-methyl-1H-indole-6-carbonyl]-amino}-methyl)-pyrrolidin-3-ylmethyl ester

((R)-1-Phenyl-propyl)-carbamic acid (3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl ester

N-[(3S*,4S*)-4-(1-Cyclopropyl-3-furan-2-ylmethyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S,4S)-4-(1-Cyclopropyl-3-furan-2-ylmethyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-(3-(4-Methoxy benzyl-1-cyclopropyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-(3-(4-Chloro benzyl-1-cyclopropyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-(3-(4-Fluoro benzyl-1-cyclopropyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-(3-Cyclohexylmethyl-1-cyclopropyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-{(3S*,4S*)-4-[1-Cyclopropyl-3-(tetrahydro-pyran-4-ylmethyl)-ureidomethyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-(1-Cyclopropyl-3-phenethyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-(1-Cyclopropyl-3,3-diphenyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-(1-Cyclopropyl-3,3-diisopropyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-(3-Benzyl-1-cyclopropyl-3-methyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-(3-Benzyl-1-cyclopropyl-3-ethyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S,4S)-4-(3-Benzyl-1-cyclopropyl-3-ethyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-(3-Benzyl-1,3-dicyclopropyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-(1-Cyclopropyl-3-phenyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-(3-Benzhydryl-1-cyclopropyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S,4S)-4-(3-Benzyl-1-cyclopropyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-(1,3-Dicyclopropyl-3-phenyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-(3-Cyclohexyl-1-cyclopropyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S*,4S*)-4-(1-Cyclopropyl-3-naphthalen-1-yl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S,4S)-4-(1-Cyclopropyl-3-naphthalen-2-yl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-{(3S,4S)-4-[1-Cyclopropyl-3-((R)-1-phenyl-propyl)-ureidomethyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-[(3S,4S)-4-(1-Cyclopropyl-3-isobutyl-3-methyl-ureidomethyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

N-{(3S,4S)-4-[1-Cyclopropyl-3-((S)-1-phenyl-propyl)-ureidomethyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

(R)-3-Phenyl-pyrrolidine-1-carboxylic acid cyclopropyl-[(3S,4S)-4-({isopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-amide

4-Ethyl-3-(3-hydroxy-propoxy)-N-isopropyl-N-{(3S,4S)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-benzamide

N-{(3S,4S)-4-[(Cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-3-(3-hydroxy-propoxy)-N-isopropyl-4-methoxy-benzamide

N-{(3S*,4S*)-4-[(Cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(4-methoxy-butyl)-benzamide

N-{(3S*,4S*)-4-[(Cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-4-difluoromethyl-N-isopropyl-3-(3-methoxy-propoxy)-benzamide

8-(3-Methoxy-propoxy)-2,3-dihydro-benzo[1,4]dioxine-6-carboxylic acid {(3S*,4S*)-4-[(cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-isopropyl-amide

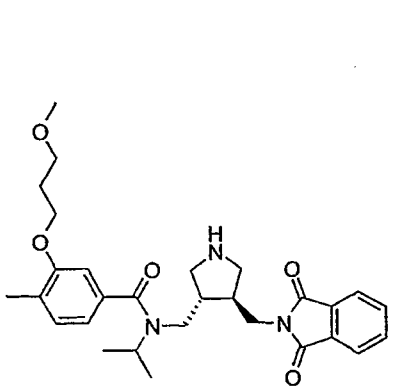
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2-Chloro-N-{(3S*,4S*)-4-[(cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-5-(3-methoxy-propoxy)-benzamide

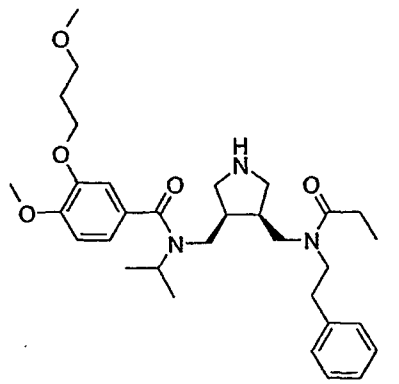
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4-Chloro-N-{(3S*,4S*)-4-[(cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-3-(3-methoxy-propoxy)-benzamide
4-tert-Butyl-N-isopropyl-3-(3-methoxy-propoxy)-N-{(3S,4S)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-benzamide
N-Isopropyl-4-methoxy-3-(2-methoxy-ethoxymethyl)-N-{(3S,4S)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-benzamide
N-Isopropyl-3-(2-methoxy-ethoxymethyl)-N-{(3S,4S)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-4-trifluoromethoxy-benzamide
N-Isopropyl-4-methoxy-N-{(3S,4S)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-3-(3,3,3-trifluoro-propoxy)-benzamide
N-Isopropyl-4-methoxy-N-{(3S,4S)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-3-(4,4,4-trifluoro-butoxy)-benzamide
N-{(3S,4S)-4-[(Cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-4-methoxy-3-(3-trifluoromethoxy-propoxy)-benzamide
N-{(3S,4S)-4-[(Cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-4-ethyl-N-isopropyl-3-(3-trifluoromethoxy-propoxy)-benzamide
N-Isopropyl-4-methoxy-3-(5-methyl-isoxazol-3-ylmethoxy)-N-{(3S,4S)-4-[(methyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-benzamide
N-{(3S,4S)-4-[(Cyclopropyl-phenylacetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-N-isopropyl-3-(2-methoxy-ethoxymethyl)-4-trifluoromethoxy-benzamide
3-(2-Ethoxy-ethoxy)-N-isopropyl-4-methoxy-N-{(3S,4S)-4-[(methyl-phenyl acetyl-amino)-methyl]-pyrrolidin-3-ylmethyl}-benzamide
N-[(3S*,4S*)-4-({Cyclopropyl-[2-(4-methoxy-phenyl)-acetyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide
N-[(3S*,4S*)-4-({Cyclopropyl-[4-methoxy-3-(3-methoxy-propoxy)-benzoyl]-amino}-methyl)-pyrrolidin-3-ylmethyl]-N-isopropyl-4-methoxy-3-(3-methoxy-propoxy)-benzamide

or a pharmaceutically acceptable salt thereof.

14. A compound of the formula



or



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15. A compound of the formula I, or a pharmaceutically acceptable salt thereof, according to any one of claims 5 to 7 or 11 to 14 for use in the diagnostic or therapeutic treatment of a warm-blooded animal.

16. A compound of the formula I, or a pharmaceutically acceptable salt thereof, according to any one of claims 5 to 7 or 11 to 14 for use according to claim 16 in the treatment of a disease that depends on activity of renin, especially hypertension.

17. The use of a compound of the formula I, or a pharmaceutically acceptable salt thereof, according to any one of claims 5 to 7 or 11 to 14 for the manufacture of a pharmaceutical composition for the treatment of a disease that depends on activity of renin, especially hypertension.

18. The use of a compound of the formula I, or a pharmaceutically acceptable salt thereof, according to any one of claims 5 to 7 or 11 to 14 for the treatment of a disease that depends on activity of renin, especially hypertension.

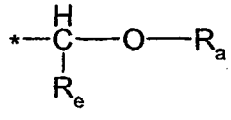
19. A pharmaceutical formulation, comprising a compound of the formula I, or a pharmaceutically acceptable salt thereof, as mentioned in any one of claims 1 to 4, 8 to 10 or preferably 5 to 7 or 11 to 14 and at least one pharmaceutically acceptable carrier material.

20. A method of treatment a disease that depends on activity of renin, comprising administering to a warm-blooded animal, especially a human, in need of such treatment a

pharmaceutically effective amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, as mentioned in any one of claims 1 to 14 or 15 or 16 or 18.

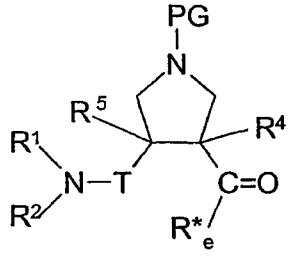
21. A process for the manufacture of a compound of the formula I, or a pharmaceutically acceptable salt thereof, according to any one of claim 4, comprising

(A) for the synthesis of a compound of the formula I wherein R^3 is a moiety of the formula (a)



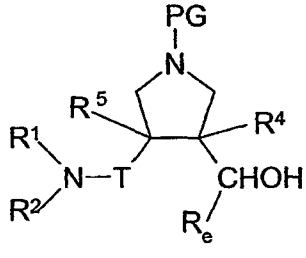
(a)

wherein R_a and R_e are as defined for a compound of the formula I and R^1, R^2, R^4, R^5 and T are as defined for a compound of the formula I, reducing a compound of the formula II,



(II)

wherein R^1, R^2, R^4, R^5 and T are as just defined, R^*_e is hydroxy or etherified hydroxyl such as OMe or R_e as defined for a compound of the formula I and PG is a protecting group, to the corresponding hydroxy compound of the formula III,



(III)

wherein R_e is as defined for a compound of the formula I and the other moieties are as defined, which is then either deprotected to a corresponding compound of the formula I wherein R_a in the moiety of the formula (a) is hydrogen or further reacted either

(i) with a compound of the formula IV,

$$R_a^*\text{-}X \qquad \text{(IV)}$$

wherein R_a^* is unsubstituted or substituted alkyl, unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-

alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-alkyl or acyl and X is a leaving group, or

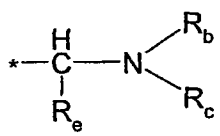
(ii) in order to introduce a moiety R_a which is N-(unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkyl or unsubstituted or substituted alkyl)-aminocarbonyl, with an isocyanato compound of the formula IV* or a chlorocarbamate of the formula $(R_a{}^{**})_2$-N-C(=O)-Cl,

$$R_a{}^{**}\text{-N=C=O} \qquad \text{(IV*)}$$

wherein $R_a{}^{**}$ is unsubstituted or substituted mono- or bicyclic aryl, unsubstituted or substituted mono- or bicyclic heterocyclyl, unsubstituted or substituted mono- or bicyclic cycloalkyl, unsubstituted or substituted mono- or bicyclic aryl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic heterocyclyl-C_1-C_7-alkyl, unsubstituted or substituted mono- or bicyclic cycloalkyl-C_1-C_7-alkyl or unsubstituted or substituted alkyl,

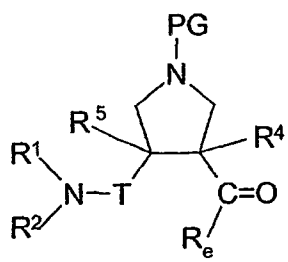
where reaction (i) or (ii) is followed by removal of any protecting group(s) to give a corresponding compound of the formula I if no further conversion requiring the presence of protecting groups is desired; or

(B) for the synthesis of a compound of the formula I wherein R^3 is a moiety of the formula (b)



(b)

wherein R_e, R_b and R_c are as defined for a compound of the formula I, and wherein R^1, R^2, R^4, R^5 and T are as defined for a compound of the formula I, reacting an aldehyde compound of the formula V,



(V)

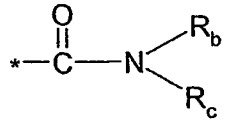
wherein R_e, R^1, R^2, R^4, R^5 and T are as defined for a compound of the formula I and PG is a protecting group,

under conditions of reductive amination with a compound of the formula VI,

$$R_b\text{-}NH\text{-}R_c \qquad (VI)$$

wherein R_b and R_c are as defined for a compound of the formula I, followed, if no further conversion requiring protecting groups is intended, by removal of any protecting group(s); or

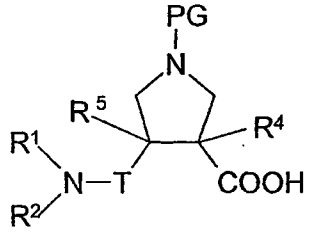
(C) for the synthesis of a compound of the formula I wherein R^3 is a moiety of the formula (f)



(f)

wherein R_b and R_c as well as R^1, R^2, R^4, R^5 and T are as defined for a compound of the formula I,

condensing an acid of the formula IIB,



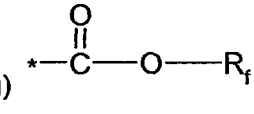
(IIB)

wherein R^1, R^2, R^4, R^5 and T are as defined for a compound of the formula I and PG is a protecting group, or a reactive derivative thereof, with an amine of the formula VI,

$$R_b\text{-}NH\text{-}R_c \qquad (VI)$$

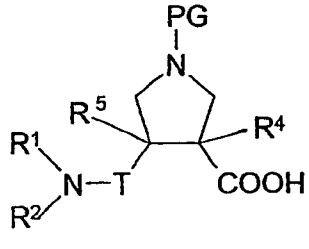
wherein R_b and R_c are as defined for a compound of the formula I, followed, if no further conversion requiring protecting groups is intended, by removal of any protecting group(s); or

(D) for the synthesis of a compound of the formula I wherein R^3 is a moiety of the formula (g)



(g)

wherein R_f is as defined for a compound of the formula I and wherein R^1, R^2, R^4, R^5 and T are as defined for a compound of the formula I, reacting an acid of the formula IIB,



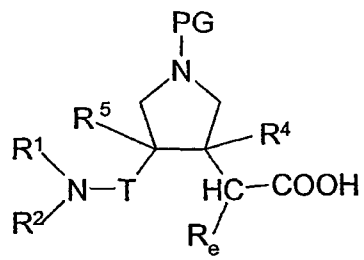
(IIB)

wherein R^1, R^2, R^4, R^5 and T are as defined for a compound of the formula I and PG is a protecting group, or a reactive derivative thereof, with an alcohol or alcohol derivative of the formula VII,

$$R_f\text{-}X \qquad \text{(VII)}$$

wherein R_f is as defined for a compound of the formula I and X is hydroxy or a leaving group, followed, if no further conversion requiring protecting groups is intended, by removal of any protecting group(s); or

(E) for the synthesis of a compound of the formula I wherein R^3 is a moiety of the formula (d) or (e) as defined for a compound of the formula I and R^1, R^2, R^4 R^5 and T are as defined for a compound of the formula I, reacting a compound of the formula IIA,



(IIA)

wherein R^1, R^2, R^4, R^5, T and R_e are as defined for a compound of the formula I,

(i) for the synthesis of a compound of the formula I wherein R^3 is a moiety of the formula (d) with a compound of the formula VI,

$$R_b\text{-}NH\text{-}R_c \qquad \text{(VI)}$$

wherein R_a and R_b are as defined for a compound of the formula I, or

(ii) for the synthesis of a compound of the formula I wherein $R^3$is a moiety of the formula (e) with a compound of the formula VII,

$$R_f\text{-}X \qquad \text{(VII);}$$

wherein R_f is as defined for a compound of the formula I and X is hydroxy or a leaving group;

and, if desired, subsequent to any one or more of the processes (A), (B), (C), (D) or (E) mentioned above, converting an obtainable compound of the formula I or a protected form thereof into a different compound of the formula I, converting a salt of an obtainable compound of formula I into the free compound or a different salt, converting an obtainable free compound of formula I into a salt thereof, and/or separating an obtainable mixture of isomers of a compound of formula I into individual isomers;

where in any of the starting materials (especially of the formulae II to VIII), in addition to specific protecting groups mentioned, further protecting groups may be present, and any protecting groups are removed at an appropriate stage in order to obtain a corresponding compound of the formula I, or a salt thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/002578

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4025 A61K31/341 A61K31/351 A61K31/357 A61K31/4035
A61K31/404 A61K31/416 A61K31/422 A61K31/423 A61K31/4409
A61K31/454 A61K31/4704 A61K31/506 A61K31/5355 A61K31/5377

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	E. SPECKER ET AL.: "An old target revisited: Two new privileged skeletons and an unexpected binding mode for HIV-protease inhibitors" ANGEWANDTE CHEMIE, INTERNATIONAL EDITION, vol. 44, no. 20, 13 May 2005 (2005-05-13), pages 3140-3144, XP002388826 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim ISSN: 1433-7851 Figure 2, Scheme 2.c page 3140, column 1, paragraph 1 page 3140, column 2, paragraph 3 - page 3141, column 1, paragraph 2 page 3144, column 1, paragraphs 2,3	11,12,15
A,P	----- -/--	1-10,13, 14,16-21

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

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

Date of the actual completion of the international search	Date of mailing of the international search report
10 July 2006	27/07/2006

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	Golebiowska, K

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CN 1 583 724 A (MEDICINE BIOLOGICAL TECHNOLOGY INST., CHINESE MEDICINE ACADEMY) 23 February 2005 (2005-02-23) abstract formula III page 4, lines 9-11 scheme on page 12 page 19, lines 1-8	1-21
A	EP 0 242 789 A (DAINIPPON PHARMACEUTICAL CO., LTD) 28 October 1987 (1987-10-28) abstract Formula B page 1, line 4 - page 2, line 3 page 10, lines 6-9 page 10, line 18 - page 11, line 13 page 29; example 20	1-21
A	WO 00/51609 A (MERCK & CO., INC; BAO, JIANMING; BAKER, ROBERT, K; PARSONS, WILLIAM, H) 8 September 2000 (2000-09-08) abstract page 145, lines 6-8 page 115, lines 5-12 page 75, line 1 - page 77, line 2; compound 21	1-21
A	TAYLOR G M ET AL: "On The Ritter Reaction of Cyclic Hydroxyamines: Synthesis of Conformationally-Restricted Reduced Amide Dipeptide Isosteres" TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 37, no. 8, 19 February 1996 (1996-02-19), pages 1297-1300, XP004030131 ISSN: 0040-4039 the whole document	1-21
A	N. D. L. FISHER AND N. K. HOLLENBERG: "Is there a future for renin inhibitors?" EXPERT OPINION ON INVESTIGATIONAL DRUGS, vol. 10, no. 3, 2001, pages 417-426, XP002388827 ISSN: 1354-3784 the whole document	1-21
A	WOOD J M ET AL: "Inhibitors of renin as potential therapeutic agents" JOURNAL OF ENZYME INHIBITION 1987 UNITED KINGDOM, vol. 1, no. 3, 1987, pages 169-185, XP009068927 the whole document	1-21

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/002578

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WOOD JEANETTE M ET AL: "Structure-based design of aliskiren, a novel orally effective renin inhibitor." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS. 5 SEP 2003, vol. 308, no. 4, 5 September 2003 (2003-09-05), pages 698-705, XP002388828 ISSN: 0006-291X the whole document	1-21

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2006/002578

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		YU	27788 A1	30-04-1990
		YU	73987 A1	31-08-1988
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WO 0051609 A	08-09-2000	AU	3386400 A	21-09-2000

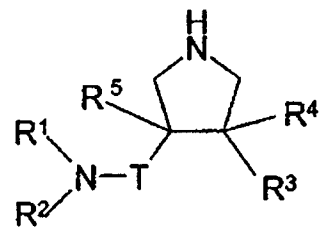
38

DERIVADOS DE PIRROLIDINA 3,4-SUSTITUIDA PARA EL TRATRAMIENTO DE HIPERTENSION

Descripción de la Invención

La invención se refiere al uso de compuestos de pirrolidina (3,4-di-, 3,3,4-tri-, 3,4,4-tri-, ó 3,3,4,4-tetra-)-sustituida para la preparación de una formulación farmacéutica para el tratamiento de una enfermedad que dependa de la actividad de la renina; al uso de un compuesto de esa clase en el tratamiento de una enfermedad que dependa de la actividad de la renina; a compuestos que son parte de una subclase de estos compuestos de pirrolidina sustituida para utilizarse en el diagnóstico y en el tratamiento terapéutico de un animal de sangre caliente, en especial para el tratamiento de una enfermedad (= trastorno) que dependa de la actividad de la renina; a nuevos compuestos que son parte de una subclase de estos compuestos de pirrolidina sustituida; a formulaciones o productos farmacéuticos que comprenden a estos compuestos de pirrolidina sustituida, y/o a un método de tratamiento que comprende administrar estos compuestos de pirrolidina sustituida, a un método para la fabricación en especial de estos nuevos compuestos de pirrolidina sustituida, así como a novedosos intermediarios, materiales de partida, y/o pasos parciales para su síntesis.

En especial, la invención se refiere al uso de un compuesto de la Fórmula I:



(I)

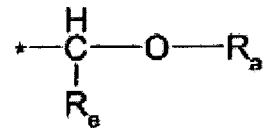
como se describe en las reivindicaciones, o en donde:

R^1 es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, alquenilo insustituido o sustituido, alquinilo insustituido o sustituido, o acilo;

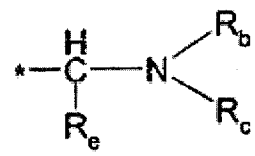
R^2 es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, alquenilo insustituido o sustituido, alquinilo insustituido o sustituido, o acilo;

R^3 es una fracción seleccionada a partir del grupo de fracciones de las fórmulas:

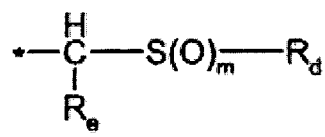
(a)



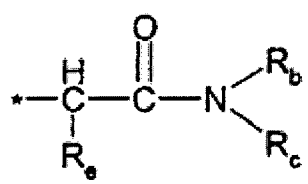
(b)



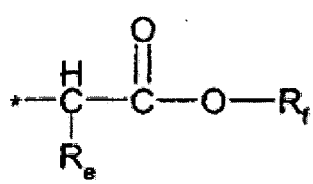
(c)



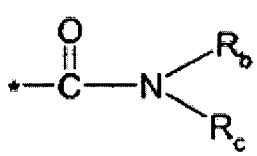
(d)



(e)

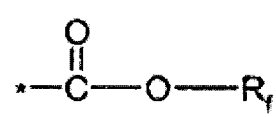


(f)



y

(g)



en donde, en cualquiera de las fracciones de las fórmulas dadas anteriormente bajo (a), (b), (c), (d), (e), (f), y (g), el

asterisco (*) muestra en enlace que enlaza a la fracción R^3 respectiva con el resto de la molécula en la Fórmula I,

R_a es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, acilo, o hidrógeno;

R_b y R_c se seleccionan independientemente a partir de las fracciones dadas en R_a, con la condición de que de preferencia no más de uno de R_b y R_c sea acilo;

R_d es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, o (de preferencia si m es 0) acilo, o puede tener uno de estos significados, o puede ser $-N(R_b(R_c)$ si m es 1 ó de preferencia 2;

R_e es hidrógeno, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, o (en especial) alquilo de 1 a 7 átomos de carbono

sustituido o de preferencia insustituido; y

R_f es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido;

m es 0, 1, ó 2;

cada uno de R^4 y R^5 se selecciona, independiente-mente uno del otro, a partir de hidrógeno, alquilo insustituido o sustituido, hidroxi, o hidroxi esterificado o eterificado;

y T es metileno (-CH_2-), metileno mono-sustituido por alquilo (-[C(H)(alquilo)]-), carbonilo (-C(=O)-), o tio-carbonilo (-C(=S)-);

o una sal farmacéuticamente aceptable del mismo,

en la preparación de una formulación farmacéutica para el tratamiento de una enfermedad que dependa de la actividad de la renina, en especial hipertensión.

Los compuestos de la presente invención exhiben una actividad inhibidora sobre la enzima natural renina. Por consiguiente, los compuestos de la Fórmula I se pueden emplear para el tratamiento (incluyendo este término también la profilaxis) de uno o más trastornos o enfermedades seleccionadas a partir de, entre otras, hipertensión, ateroesclerosis, síndrome coronario

inestable, insuficiencia cardíaca congestiva, hipertrofia cardíaca, fibrosis cardíaca, cardiomiopatía posterior a infarto, síndrome coronario inestable, disfunción diastólica, enfermedad crónica del riñón, fibrosis hepática, complicaciones resultantes de diabetes, tales como nefropatía, vasculopatía y neuropatía, enfermedades de los vasos coronarios, restenosis en seguida de angioplastía, presión intra-ocular elevada, glaucoma, crecimiento vascular anormal, hiperaldosteronismo, deterioro cognoscitivo, enfermedad de Alzheimer, demencia, estados de ansiedad y trastornos cognoscitivos, en especial hasta donde se puedan modular (más especialmente influenciar de una manera benéfica) estas enfermedades mediante la inhibición de la renina.

En las reivindicaciones y más adelante se enlistan las definiciones de diferentes términos utilizados para describir los compuestos de la presente invención, así como su uso y síntesis, materiales de partida e intermediarios, y similares. Estas definiciones, ya sea mediante el reemplazo de una, más de una, o todas las expresiones o símbolos generales utilizados en la presente divulgación, y que por lo tanto produzcan las modalidades preferidas de la invención, se aplican de preferencia a los términos como se utilizan a través de toda la memoria descriptiva, a menos que sean de otra manera limitados en casos específicos, ya sea individualmente o bien como parte de un grupo más grande.

El término "inferior" o "de 1 a 7 átomos de carbono" define

una fracción con hasta e incluyendo máximo 7, en especial hasta e incluyendo máximo 4 átomos de carbono, estando esta fracción ramificada (una o más veces) o de una sola cadena y enlazada por medio de un átomo de carbono terminal o no terminal. Alquilo inferior o de 1 a 7 átomos de carbono, por ejemplo, es pentilo normal, hexilo normal, o heptilo normal, o de preferencia alquilo de 1 a 4 átomos de carbono, en especial como metilo, etilo, propilo normal, propilo secundario, butilo normal, isobutilo, butilo secundario, butilo terciario.

Halo o halógeno es de preferencia flúor, cloro, bromo o yodo, más preferiblemente flúor, cloro o bromo. Si no se menciona de una manera explícita o implícita de otra forma, halógeno también puede significar más de un sustituyente de halógeno en fracciones tales como alquilo, alcanoílo, o similares (por ejemplo, en trifluorometilo, tri-fluoroacetilo).

Arilo mono- o bi-cíclico insustituido o sustituido es de preferencia un arilo mono- o bi-cíclico con 6 a 22 átomos de carbono, en especial fenilo, indenilo o naftilo, y está insustituido o sustituido por una o más, en especial por una a tres fracciones, de preferencia independientemente seleccionadas a partir del grupo que consiste en:

un sustituyente de la Fórmula -(alquileno de 0 a 7 átomos de carbono)-$(X)_r$-(alquileno de 1 a 7 átomos de carbono)-$(Y)_s$-(alquileno de 0 a 7 átomos de carbono)-H (en especial en arilo sustituido o aril-alquilo sustituido como R^1), en donde alquileno de

0 átomos de carbono significa que está presente un enlace en lugar de alquileno enlazado, y alquileno en cada caso puede ser de cadena recta o ramificada, y puede estar insustituido o (con menor preferencia) sustituido, por ejemplo, por una o más fracciones como se definen para alquilo sustituido, en especial por halógeno, especialmente flúor, hidroxi, alcoxilo de 1 a 7 átomos de carbono, feniloxilo, naftiloxilo, alcanoiloxilo de 1 a 7 átomos de carbono, benzoiloxilo, naftoiloxilo, amino, mono- o di-(alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono, fenil-alcanoílo de 1 a 7 átomos de carbono, naftil-alcanoílo de 1 a 7 átomos de carbono, fenilo, naftilo, fenil-alquilo de 1 a 7 átomos de carbono, y/o naftil-alquilo de 1 a 7 átomos de carbono)-amino, carboxilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, o ciano; **r** y **s**, cada uno independiente-mente del otro, son 0 ó 1, y cada uno de X e Y, si están presentes e independientemente de los otros, es -O-, -NV-, -S-, -O-CO-, -CO-O-, -NV-CO-; -CO-NV-; -NV-SO_2-; -SO_2-NV; -NV-CO-NV-, -NV-CO-O-, -O-CO-NV-, -NV-SO_2-NV-, en donde V es hidrógeno o alquilo insustituido o sustituido como se define más adelante, en especial alquilo de 1 a 7 átomos de carbono, o es fenilo, naftilo, fenil- o naftil-alquilo de 1 a 7 átomos de carbono, o halo-alquilo de 1 a 7 átomos de carbono; por ejemplo, alquilo de 1 a 7 átomos de carbono, tal como metilo, etilo, propilo normal, isopropilo, butilo normal, isobutilo, butilo secundario, o butilo terciario, halo-alquilo de 1 a 7 átomos de carbono, tal como trifluorometilo, hidroxi-alquilo de 1 a 7 átomos

de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, tal como 3-metoxi-propilo ó 2-metoxi-etilo, alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, feniloxi- o naftiloxi-alquilo de 1 a 7 átomos de carbono, alcanoiloxilo de 1 a 7 átomos de carbono- alquilo de 1 a 7 átomos de carbono, amino-alquilo de 1 a 7 átomos de carbono, tal como amino-metilo, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-amino-alquilo de 1 a 7 átomos de carbono, mono- o di- (alquilo de 1 a 7 átomos de carbono, naftil, fenil, naftil-alquilo de 1 a 7 átomos de carbono, y/o fenil-alquilo de 1 a 7 átomos de carbono)-amino-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono-amino-alquilo de 1 a 7 átomos de carbono, alquilo de 1 a 7 átomos de carbono-O-CO-NH-alquilo de 1 a 7 átomos de carbono, alquilo de 1 a 7 átomos de carbono-sulfonil-amino-alquilo de 1 a 7 átomos de carbono, alquilo de 1 a 7 átomos de carbono-NH-CO-NH-alquilo de 1 a 7 átomos de carbono, alquilo de 1 a 7 átomos de carbono-NH-SO_2-NH-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono, hidroxi-alcoxilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono, alcanoiloxilo de 1 a 7 átomos de carbono, halo-alcoxilo de 1 a 7 átomos de carbono, tal como fluoro-metoxilo, fenil- o naftil-alcanoiloxilo de 1 a 7 átomos de carbono, fenil- o naftil-alquilo de 1 a 7 átomos de carbono-amino-carboniloxilo, halo-tioalquilo de 1 a 7 átomos de carbono, tal como

trifluoro-tiometilo, fenil- o naftil-tioalquilo de 1 a 7 átomos de carbono, mono- o di-(alquilo de 1 a 7 átomos de carbono-, naftil-alquilo de 1 a 7 átomos de carbono-, fenil-alquilo de 1 a 7 átomos de carbono-, y/o alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-)amino, alcanoílo de 1 a 7 átomos de carbono-amino, alquilo de 1 a 7 átomos de carbono-sulfonil-amino, fenil- o naftil-alcanoílo de 1 a 7 átomos de carbono-amino, fenil- o naftil-alquilo de 1 a 7 átomos de carbono-amino-carbonil-amino, carboxi-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-carbonilo, hidroxi-alcoxilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono-carbonilo, amino-alcoxilo de 1 a 7 átomos de carbono-carbonilo, (N-) mono-(alquilo de 1 a 7 átomos de carbono)-amino-alcoxilo de 1 a 7 átomos de carbono-carbonilo, alcanoílo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono-carbonilo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, naftil-alquilo de 1 a 7 átomos de carbono, y/o fenil-alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, alquilo de 1 a 7 átomos de carbono-sulfonilo, halo-alquilo de 1 a 7 átomos de carbono-sulfonilo, hidroxi-alquilo de 1 a 7 átomos de carbono-sulfonilo, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-sulfonilo, amino-alquilo de 1 a 7 átomos de carbono-sulfonilo, N-mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino-alquilo de 1 a 7 átomos de carbono-sulfonilo, alcanoílo de 1 a 7 átomos de carbono-amino-alquilo de 1 a 7

átomos de carbono-sulfonilo, N-alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-carbamoílo, o N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino-sulfonilo;

a partir de alquenilo de 2 a 7 átomos de carbono, alquinilo de 2 a 7 átomos de carbono, fenilo, naftilo, hetero-ciclilo mono- o bi-cíclico, en especial como se define más adelante para heterociclilo mono- o bi-cíclico, de preferencia seleccionado a partir de pirrolilo, furanilo, tienilo, pirimidin-2,4-dion-1-, -3-, ó -5-ilo y tetrahidrofuranilo, fenil- o naftil-, o (heterociclilo mono- o bi-cíclico)-alquilo de 1 a 7 átomos de carbono o alquiloxilo de 1 a 7 átomos de carbono, en donde heterociclilo mono- o bi-cíclico es como se define más adelante, de preferencia seleccionado a partir de pirrolilo, furanilo, tetrahidrofuranilo, tetrahidropiranilo, y tienilo; tal como bencilo o naftil-metilo, tetrahidro-furanil- o tetrahidro-piranil-alquiloxilo de 1 a 7 átomos de carbono-carbonilo, benzoil- o naftoil-amino-alquilo de 1 a 7 átomos de carbono, (fenil- o naftil- o heterociclilo mono- o bi-cíclico)-sulfonil-amino-alquilo de 1 a 7 átomos de carbono, en donde fenilo o naftilo o heterociclilo mono- o bi-cíclico está insustituido o sustituido, de preferencia por una o más, en especial por una a tres fracciones de alquilo de 1 a 7 átomos de carbono, (fenil o naftil o heterociclilo mono- o bi-cíclico)-alquilo de 1 a 7 átomos de carbono-sulfonil-amino-alquilo de 1 a 7 átomos de carbono, halógeno, hidroxi, fenil-alcoxilo de 1 a 7 átomos de carbono en donde el fenilo está de preferencia

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insustituido o sustituido, de preferencia por alcoxilo de 1 a 7 átomos de carbono y/o halógeno, heterociclilo mono- o bi-cíclico-alcoxilo de 1 a 7 átomos de carbono, (heterociclilo mono- o bi-cíclico o fenil o naftil)-oxilo, naftil-alquiloxilo de 1 a 7 átomos de carbono, (benzoil o naftoil o heterociclilo mono- o bi-cíclico-carbonil)-oxilo, (fenil o naftil o hetero-ciclilo mono- o bi-cíclico)-amino-carboniloxilo, (fenil o naftil o heterociclilo mono- o bi-cíclico)-tio, (benzoil o naftoil o heterociclilo mono- o bi-cíclico)-tio, nitro, amino, di-((naftil o fenil o heterociclilo mono- o bi-cíclico)-alquilo de 1 a 7 átomos de carbono)-amino, (benzoil o naftoil o heterociclilo mono- o bi-cíclico)-amino, (fenil o naftil o heterociclilo mono- o bi-cíclico)-sulfonil-amino, en donde el fenilo o naftilo está insustituido o sustituido, de preferencia por una o más, en especial por una a tres fracciones de alquilo de 1 a 7 átomos de carbono, (fenil o naftil o heterociclilo mono- o bi-cíclico)-alquilo de 1 a 7 átomos de carbono-sulfonil-amino, (fenil o naftil o heterociclilo mono- o bi-cíclico)-amino-carbonil-amino, (fenil o naftil o heterociclilo mono- o bi-cíclico)-oxicarbonil-amino, (fenil o naftil o heterociclilo mono- o bi-cíclico)-alquiloxilo de 1 a 7 átomos de carbono-carbonil-amino, carboxilo, alquilo de 1 a 7 átomos de carbono-carbonilo, halo-alquilo de 1 a 7 átomos de carbono-carbonilo, hidroxi-alquilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-carbonilo, amino-alquilo de 1 a 7 átomos de carbono-carbonilo, (N-) mono- o (N,N-) di-(alquilo de 1 a 7 átomos

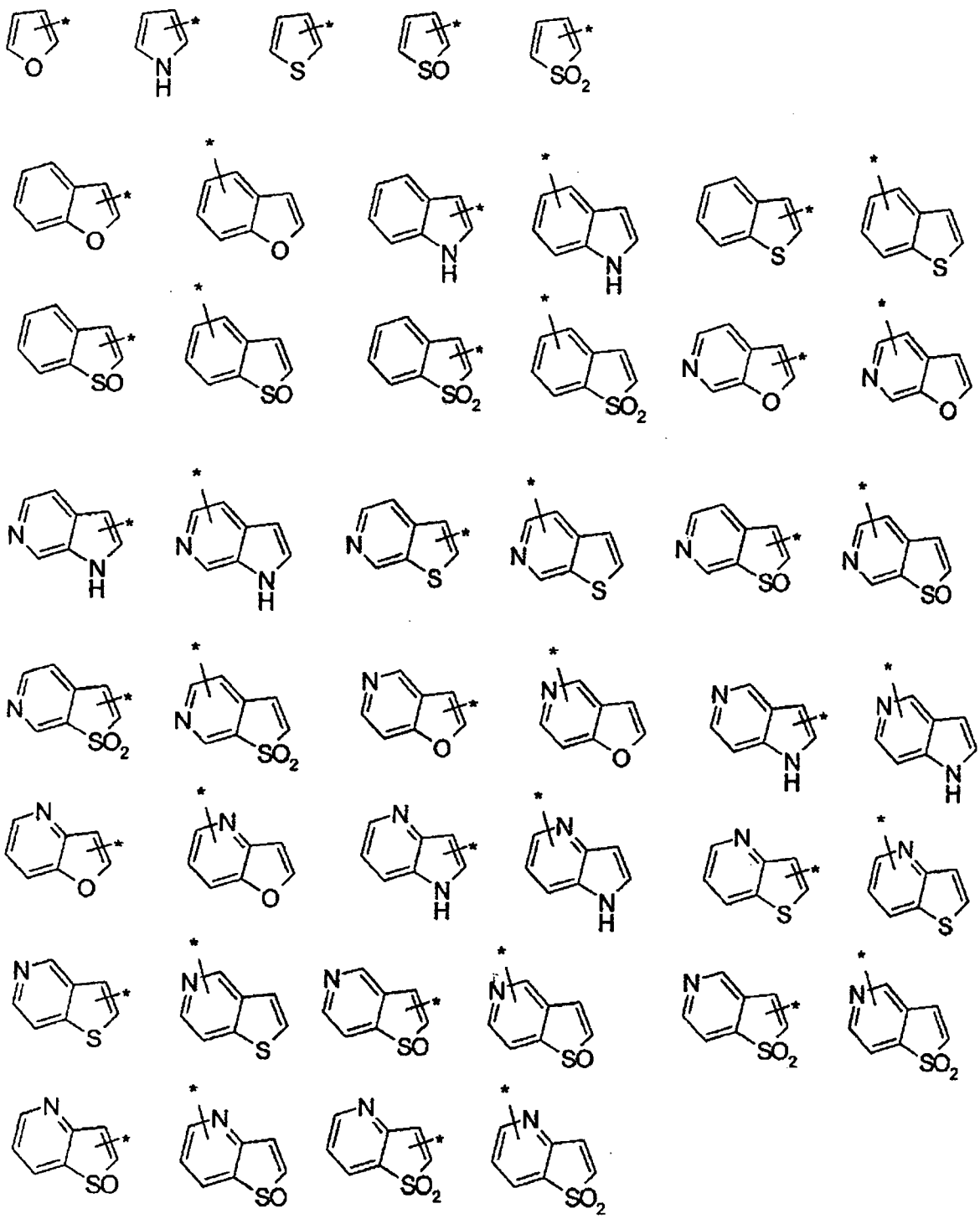
de carbono)-amino-alquilo de 1 a 7 átomos de carbono-carbonilo, alcanoílo de 1 a 7 átomos de carbono-amino-alquilo de 1 a 7 átomos de carbono-carbonilo, halo-alcoxilo de 1 a 7 átomos de carbono-carbonilo, (fenil o naftil o heterociclilo mono- o bi-cíclico)-oxi-carbonilo, (fenil o naftil o heterociclilo mono- o bi-cíclico)-alcoxilo de 1 a 7 átomos de carbono-carbonilo, (N,N-) di-(alquilo de 1 a 7 átomos de carbono)-amino-alcoxilo de 1 a 7 átomos de carbono-carbonilo, carbamoílo, N-mono- o N,N-di-(naftil o fenil o heterociclilo mono- o bi-cíclico)-amino-carbonilo, ciano, alquileno de 1 a 7 átomos de carbono que está insustituido o sustituido por hasta cuatro sustituyentes de alquilo de 1 a 7 átomos de carbono, y enlazado a dos átomos adyacentes del anillo de la fracción de arilo, sulfenilo, sulfinilo, alquilo de 1 a 7 átomos de carbono-sulfinilo, (fenil o naftil o heterociclilo mono- o bi-cíclico)-sulfinilo en donde el fenilo o naftilo está insustituido o sustituido de preferencia por una o más, en especial por una a tres fracciones de alquilo de 1 a 7 átomos de carbono, fenil- o naftil-alquilo de 1 a 7 átomos de carbono-sulfinilo, sulfonilo, (fenil o naftil o heterociclilo mono- o bi-cíclico)-sulfonilo en donde el fenilo o naftilo está insustituido o sustituido de preferencia por una o más, en especial por una a tres fracciones de alquilo de 1 a 7 átomos de carbono, (fenil o naftil o heterociclilo mono- o bi-cíclico)-alquilo de 1 a 7 átomos de carbono-sulfonilo, sulfamoílo, y N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, fenil, naftil, heterociclilo mono- o bi-cíclico, fenil-alquilo de 1 a 7 átomos de carbono, naftil-

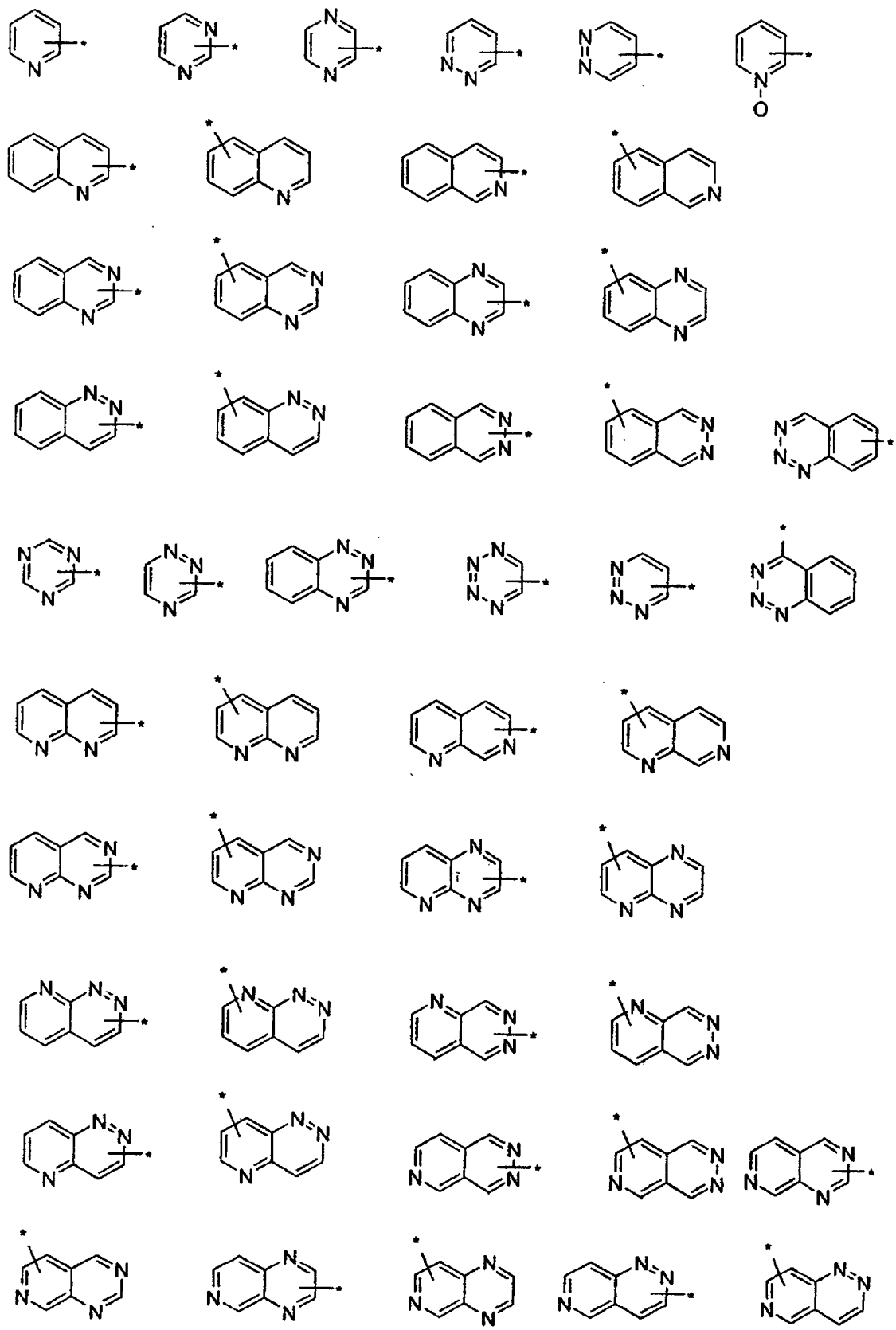
alquilo de 1 a 7 átomos de carbono, y/o heterociclilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono)-amino-sulfonilo;

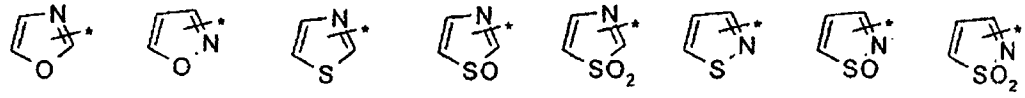
en donde cualquier fenilo o naftilo o heterociclilo mono- o bi-cíclico (cuyo heterociclilo mono- o bi-cíclico de preferencia es como se define para heterociclilo mono- o bi-cíclico, más preferiblemente se selecciona a partir de pirrolilo, furanilo, tetrahidrofuranilo, tetrahidropiranilo, y tienilo), mencionado como sustituyente de, o como parte de un sustituyente de arilo sustituido, está insustituido o sustituido por una o más, de preferencia hasta tres fracciones independientemente seleccionadas a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono, alquenilo de 1 a 7 átomos de carbono, alquinilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, tal como trifluoro-metilo, halógeno, en especial flúor, cloro, bromo o yodo, hidroxi, alcoxilo de 1 a 7 átomos de carbono, feniloxilo, naftiloxilo, fenil- o naftil-alcoxilo de 1 a 7 átomos de carbono, alcanoiloxilo de 1 a 7 átomos de carbono, fenil- o naftil-alcanoiloxilo de 1 a 7 átomos de carbono, amino, mono- o di-(alquilo de 1 a 7 átomos de carbono, fenil, naftil, fenil-alquilo de 1 a 7 átomos de carbono, naftil-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono, y/o fenil- o naftil-alcanoílo de 1 a 7 átomos de carbono)-amino, carboxilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, fenoxi-carbonilo, naftiloxi-carbonilo, fenil-alquiloxilo de 1 a 7 átomos de carbono-carbonilo, naftil-alcoxilo de 1 a 7 átomos de carbono-carbonilo, carbamoílo, N-

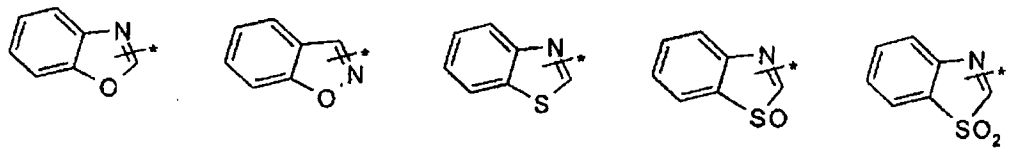
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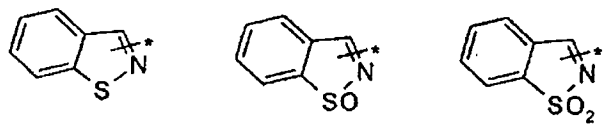
mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, fenil, naftil, fenil-alquilo de 1 a 7 átomos de carbono, y/o naftil-alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, ciano, sulfo, sulfamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, fenil, naftil, fenil-alquilo de 1 a 7 átomos de carbono, y/o naftil-alquilo de 1 a 7 átomos de carbono)-amino-sulfonilo, y nitro, o de preferencia, en donde se mencionan los sustituyentes preferidos, por uno o más de estos sustituyentes mencionados. Heterociclilo mono- o bi-cíclico insustituido o sustituido es una fracción heterocíclica mono- o bi-cíclica con un sistema de anillo insaturado, parcialmente saturado, o saturado, de preferencia con 3 a 22 (más preferiblemente 3 a 14) átomos del anillo, y con uno o más, de preferencia de uno a cuatro heteroátomos independientemente seleccionados a partir de nitrógeno (=H-, -NH-, o -NH- sustituido), oxígeno, y azufre (-S-, S(=O)-, ó S-$(=O)_2$-) que está insustituido o sustituido por uno o más, por ejemplo hasta tres sustituyentes de preferencia independientemente seleccionados a partir de los sustituyentes mencionados anteriormente para arilo y a partir de oxo (=O) y tioxo (=S). De una manera preferible, heterociclilo mono- o bi-cíclico insustituido o sustituido se selecciona a partir de las siguientes fracciones:

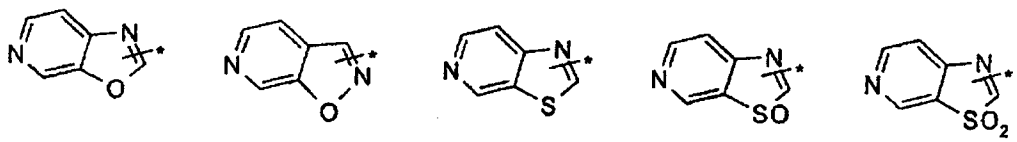

O
NH
S
SO
SO2
N
O
NH
S
SO
SO2
N
O
NH
S
SO
SO2
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SO2

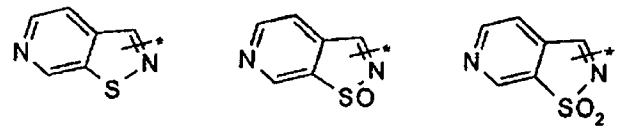


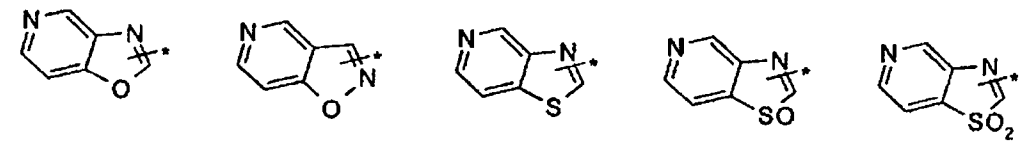


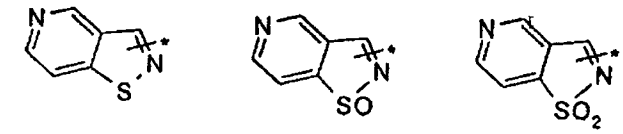


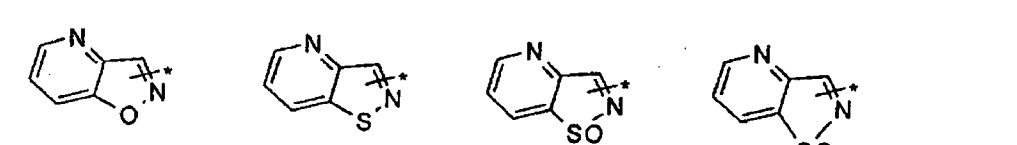


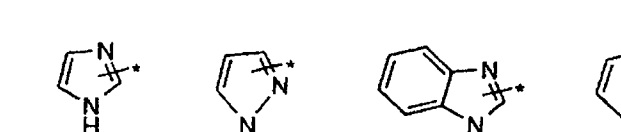


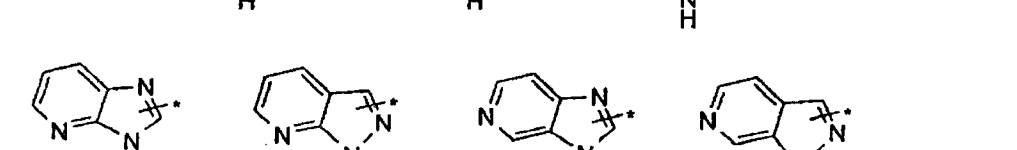


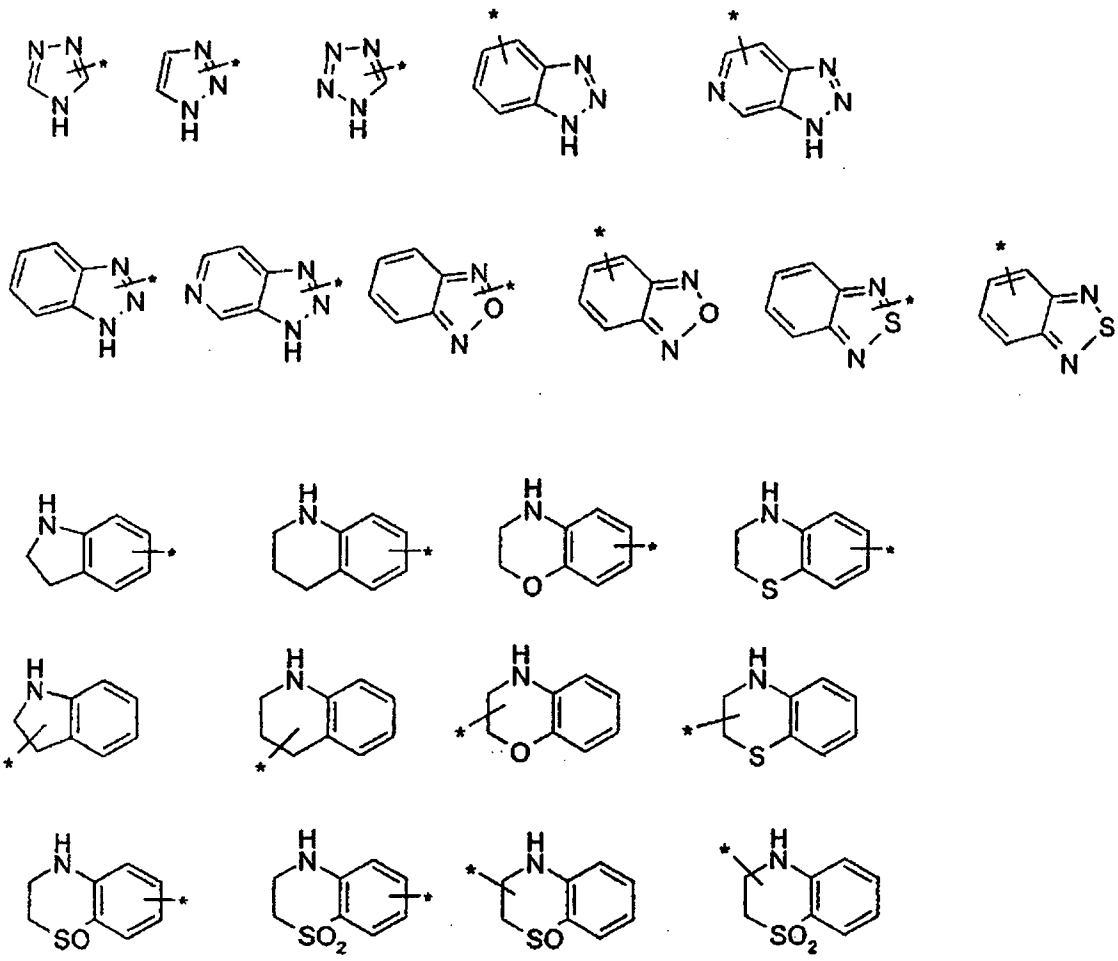


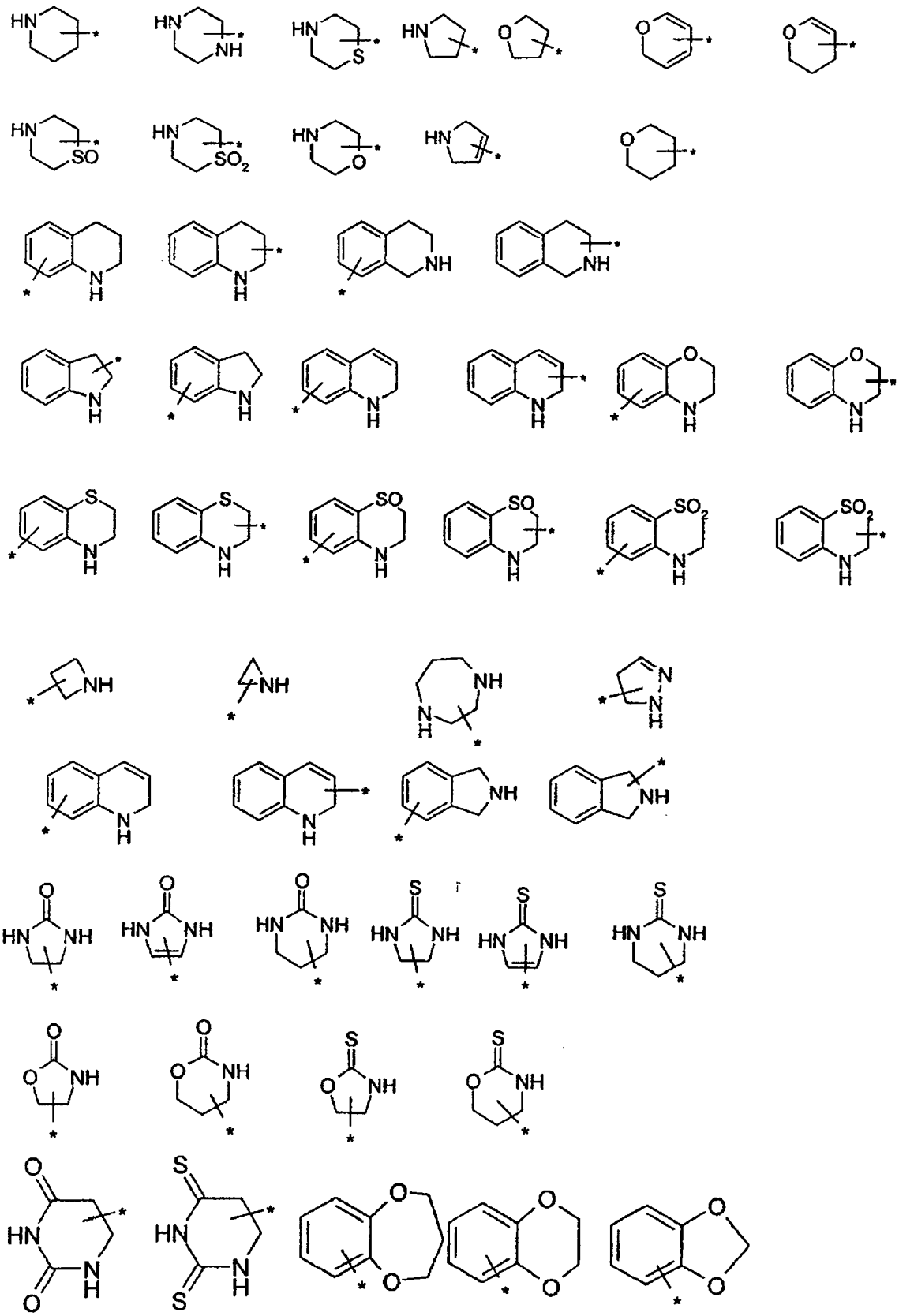


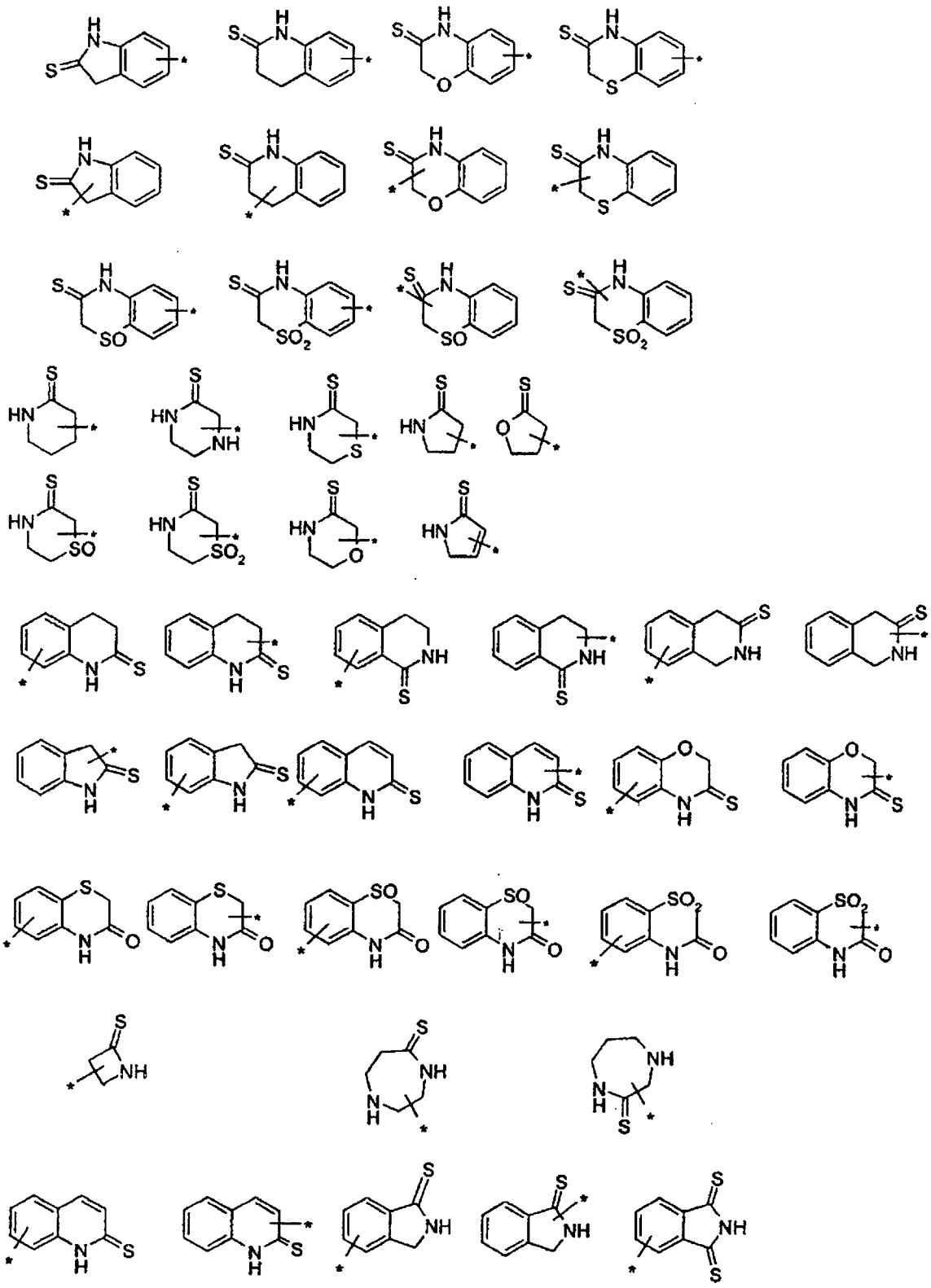


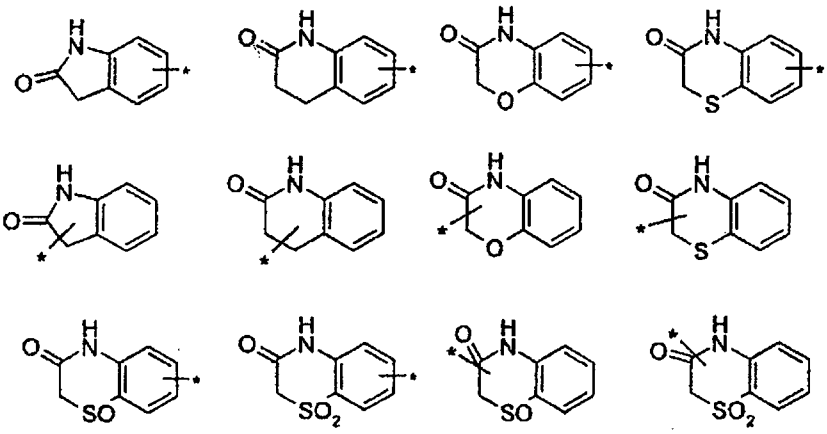


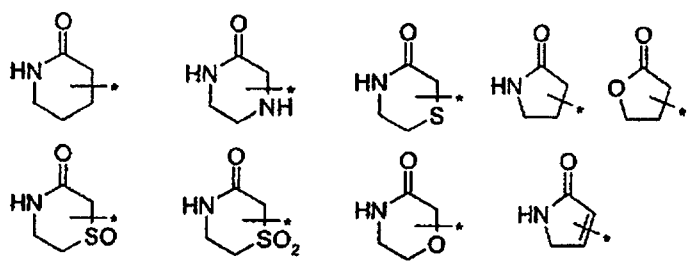


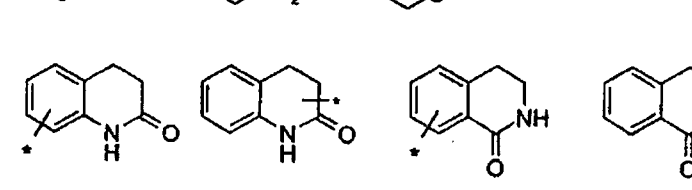


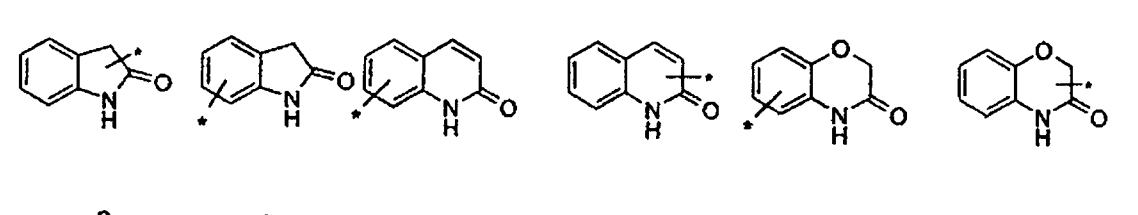


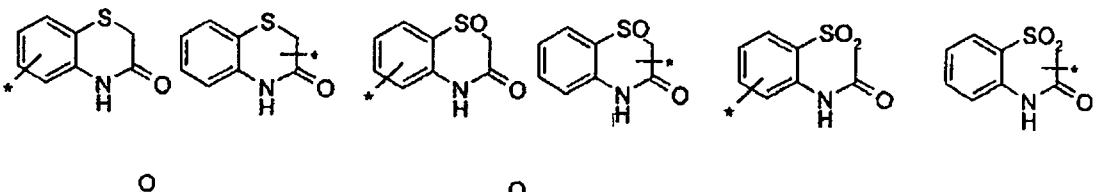


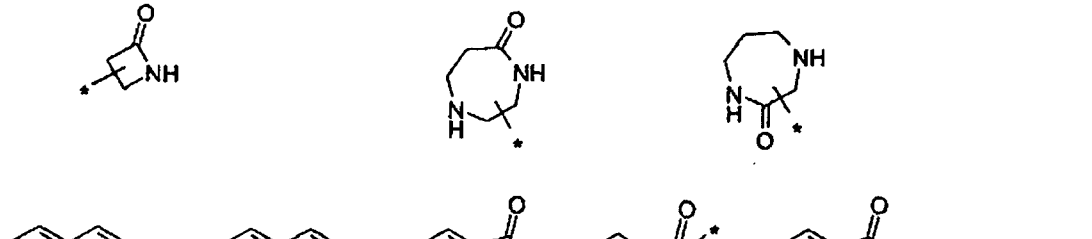




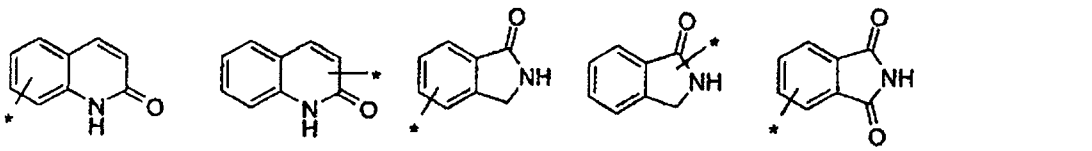














en donde, en cada caso, donde esté presente un NH, y el enlace con el asterisco que conecta a la fracción de heterociclilo respectiva con el resto de la molécula, el H puede ser reemplazado con este enlace, y/o el H puede ser reemplazado por un sustituyente (formando de esta manera imino sustituido), y puede haber uno o más sustituyentes como justamente se describió.

Cicloalquilo mono- o bi-cíclico insustituido o sustituido es de preferencia cicloalquilo mono- o bi-cíclico, más preferiblemente mono-cíclico, de 3 a 16 átomos de carbono, más preferiblemente de 3 a 10 átomos de carbono, el cual puede incluir uno o más dobles (por ejemplo en cicloalquenilo) y/o triples enlaces (por ejemplo en ciclo-alquinilo) con menos dobles y/o triples enlaces que los requeridos para formar un sistema de anillo (por ejemplo arilo) completamente insaturado. De preferencia, el ciclo-alquilo mono- o bi-cíclico está saturado. El cicloalquilo mono- o bi-cíclico está insustituido o sustituido por uno o más, por ejemplo por uno a tres sustituyentes de preferencia independientemente seleccionados a partir de aquéllos mencionados anteriormente como sustituyentes para arilo.

En arilo mono- o bi-cíclico-alquilo o -alquilo de 1 a 7 átomos de carbono insustituido o sustituido, el arilo mono- o bi-cíclico (el cual de preferencia está insustituido o sustituido por uno o más sustituyentes, por ejemplo por uno a tres sustituyentes independientemente seleccionados a partir de aquéllos mencionados anteriormente como sustituyentes para arilo), de

preferencia es como se describe en lo anterior para arilo, y está enlazado a alquilo, de preferencia alquilo de 1 a 7 átomos de carbono, ya sea terminalmente o bien en cualquier otro átomo de carbono de la cadena de alquilo, por ejemplo en el átomo de carbono en la posición 1; en donde el alquilo de 1 a 7 átomos de carbono está de otra manera insustituido o sustituido como se describe más adelante para alquilo insustituido o sustituido y/o con arilo mono- o bi-cíclico insustituido o sustituido como se describe en lo anterior.

En heterociclilo mono- o bi-cíclico-alquilo o -alquilo de 1 a 7 átomos de carbono, el heterociclilo mono- o bi-cíclico es de preferencia como se describe anteriormente, y está insustituido o sustituido por uno o más, por ejemplo hasta tres sustituyentes independientemente seleccionados a partir de aquéllos mencionados en lo anterior para arilo sustituido, y el heterociclilo está enlazado a alquilo, de preferencia alquilo de 1 a 7 átomos de carbono, ya sea terminalmente o bien en cualquier otro átomo de carbono de la cadena de alquilo, por ejemplo en el átomo de carbono en la posición 1; en donde el alquilo de 1 a 7 átomos de carbono está de otra manera insustituido o sustituido como se describe más adelante para alquilo insustituido o sustituido y/o con arilo mono- o bi-cíclico insustituido o sustituido como se describe en lo anterior.

En cicloalquilo mono- o bi-cíclico-alquilo o -alquilo de 1 a 7 átomos de carbono, el cicloalquilo mono- o bi-cíclico es de

preferencia como se describe anteriormente, y está insustituido o sustituido por uno o más, por ejemplo hasta tres sustituyentes independientemente seleccionados a partir de aquéllos mencionados en lo anterior para arilo sustituido, y el cicloalquilo está enlazado a alquilo, de preferencia alquilo de 1 a 7 átomos de carbono, ya sea terminalmente o bien en cualquier otro átomo de carbono de la cadena de alquilo, por ejemplo en el átomo de carbono en la posición 1; en donde el alquilo de 1 a 7 átomos de carbono está de otra manera insustituido o sustituido como se describe más adelante para alquilo insustituido o sustituido y/o con arilo mono- o bi-cíclico insustituido o sustituido como se describe en lo anterior.

Acilo es de preferencia arilo mono- o bi-cíclico-carbonilo o -sulfonilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-carbonilo o -sulfonilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-carbonilo o -sulfonilo insustituido o sustituido, formilo o (alquilo insustituido o sustituido, arilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, o cicloalquilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido)-carbonilo o -sulfonilo, o (en especial si está enlazado con N, S, u O) alquiloxi-carbonilo insustituido o sustituido, arilo mono- o bi-cíclico-oxi-carbonilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-oxicarbonilo insustituido o sustituido, cicloalquilo mono- o bi-

cíclico-oxicarbonilo insustituido o sustituido, arilo mono- o bi-cíclico-oxilo de 1 a 7 átomos de carbono-carbonilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-oxilo de 1 a 7 átomos de carbono-carbonilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-oxilo de 1 a 7 átomos de carbono-carbonilo insustituido o sustituido, o N-mono- o N,N-di-(arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, y/o alquilo insustituido o sustituido)-amino-carbonilo o -amino-sulfonilo, con la condición de que la fracciones enlazadas con -oxicarbonilo de preferencia estén enlazadas a un átomo de nitrógeno en el resto de la molécula. Los ejemplos de las fracciones de acilo preferidas diferentes de R^1 y/o R^2 (por ejemplo, R_a, R_b, R_c, y/o R_d), son alcanoílo de 1 a 7 átomos de carbono (tal como acetilo, 3,3-dimetil-butirilo, 2,2-dimetil-propionilo, ó 3,3-dimetil-butirilo), fenil-alcanoílo de 1 a 7 átomos de carbono insustituido (o mono-, di-, o tri-sustituido por (halógeno, alcoxilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono-alquiloxilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, y/o alquilo de 1 a 7 átomos de carbono)) (por ejemplo, el benzoílo o

fenil-acetilo insustituido o sustituido correspondiente), tal como benzoílo o fenil-acetilo, ciclo-alquilo de 3 a 8 átomos de carbono-carbonilo, o cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono-carbonilo, tal como ciclopropil-carbonilo, ciclobutil-carbonilo, ciclohexil-acetilo, o ciclohexil-carbonilo, (tetra-hidrofuranil o tetra-hidropiranil)-carbonilo, o (tetrahidro-furanil o tetrahidropiranil)-alquilo de 1 a 7 átomos de carbono-carbonilo, tal como tetrahidrofuranil-carbonilo, tetra-hidropiranil-carbonilo, tetrahidro-furanil-acetilo o tetrahidro-piranil-acetilo, (fenil- o fenil-alquilo de 1 a 7 átomos de carbono)-sulfonilo insustituido o mono-, di-, o tri-sustituido por (halógeno y/o alquilo de 1 a 7 átomos de carbono), tal como fenil-sulfonilo (= bencensulfonilo) o fenil-metan-sulfonilo, alquilo de 1 a 7 átomos de carbono-sulfonilo, tal como metil-sulfonilo (= metan-sulfonilo), ((N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, N-[fenilo o fenil-alquilo de 1 a 7 átomos de carbono (por ejemplo bencil)]-amino-carbonilo, N-[cicloalquilo de 3 a 8 átomos de carbono (por ejemplo, ciclohexilo-), cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono]-amino-carbonilo, alquilo de 1 a 7 átomos de carbono-amino-carbonilo o (alquilo de 1 a 7 átomos de carbono, fenil, naftil, fenil-alquilo de 1 a 7 átomos de carbono, naftil-alquilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono, y/o heterociclilo mono- o bi-cíclico seleccionado de preferencia a partir de pirrolilo,

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furanilo, tienilo (= tiofenilo), tiazolilo, pirazolilo, triazolilo, tetrazolilo, oxetidinilo, 3-(alquilo de 1 a 7 átomos de carbono)-oxetidinilo, piridilo, pirimidinilo, morfolino, tiomorfolino, piperidinilo, piperazinilo, pirrolidinilo, tetra-hidrofuran-onilo, tetrahidro-piranilo, 1H-indazanilo, benzo-furanilo, benzo-tiofenilo, (más preferiblemente) isoquinolinilo, quinolinilo, e indolilo)-oxicarbonilo, por ejemplo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, tal como terbutiloxi-carbonilo, isobutiloxi-carbonilo, o fenil-alquiloxilo de 1 a 7 átomos de carbono-carbonilo. Como acilo R^1 o R^2, indolil-alcanoílo de 1 a 7 átomos de carbono, por ejemplo indolil-carbonilo, quinolil-alcanoílo de 1 a 7 átomos de carbono, por ejemplo quinolinil-carbonilo, o fenil-alcanoílo de 1 a 7 átomos de carbono, por ejemplo fenil-acetilo, en donde indolilo, quinolilo, y fenilo están insustituidos o sustituidos por un sustituyente de la Fórmula -(alquileno de 0 a 7 átomos de carbono)-$(X)_r$-(alquileno de 1 a 7 átomos de carbono)-$(Y)_s$-(alquileno de 0 a 7 átomos de carbono)-H, en donde alquileno de 0 átomos de carbono significa que está presente un enlace en lugar de alquileno enlazado, y alquileno puede ser en cada caso de cadena recta o ramificada, y puede estar insustituido o (con menor preferencia) sustituido, por ejemplo, por una o más fracciones como se definen para alquilo sustituido, en especial por halógeno, especialmente flúor, hidroxi, alcoxilo de 1 a 7 átomos de carbono, feniloxilo, naftiloxilo, alcanoiloxilo de 1 a 7 átomos de carbono, benzoiloxilo, naftoiloxilo, amino, mono- o di-(alquilo de 1 a 7 átomos de

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carbono, alcanoílo de 1 a 7 átomos de carbono, fenilo, naftilo, fenil-alquilo de 1 a 7 átomos de carbono, y/o naftil-alquilo de 1 a 7 átomos de carbono)-amino, carboxilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, o ciano; r y s, cada uno independientemente del otro, son 0 ó 1, y cada uno de X e Y, si están presentes e independientemente de los otros, es -O-, -NV-, -S-, -O-CO-, -CO-O-, -NV-CO-; -CO-NV-; -NV-SO_2-; -SO_2-NV; -NV-CO-NV-, -NV-CO-O-, -O-CO-NV-, -NV-SO_2-NV-, en donde V es hidrógeno o alquilo insustituido o sustituido como se define más adelante, en especial alquilo de 1 a 7 átomos de carbono, o es fenilo, naftilo, fenil- o naftil-alquilo de 1 a 7 átomos de carbono, o halo-alquilo de 1 a 7 átomos de carbono; y opcionalmente uno o más, por ejemplo hasta dos sustituyentes adicionales seleccionados a partir de los otros sustituyentes mencionados para arilo sustituido. arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido y cicloalquilo mono- o bi-cíclico insustituido o sustituido son de preferencia como se definen anteriormente siempre que se mencionen como parte de acilo, y alquilo insustituido o sustituido es de preferencia como se define más adelante.

Alquilo insustituido o sustituido es de preferencia alquilo de 1 a 20 átomos de carbono, más preferiblemente alquilo de 1 a 7 átomos de carbono, es decir, de cadena recta o ramificada (una o, donde sea apropiado, más veces), el cual está insustituido o sustituido por una o más, por ejemplo hasta tres fracciones

seleccionadas a partir de heterociclilo mono- o bi-cíclico insustituido o sustituido como se describe más adelante, en especial pirrolilo, furanilo, tienilo (= tiofenilo), tiazolilo, pirazolilo, triazolilo, tetrazolilo, oxetidinilo, 3-(alquilo de 1 a 7 átomos de carbono)-oxetidinilo, piridilo, pirimidinilo, morfolino, tiomorfolino, piperidinilo, piperazinilo, pirrolidinilo, tetrahidrofuran-onilo, tetrahidro-piranilo, 1H-indazanilo, benzo-furanilo, benzo-tiofenilo, (más preferiblemente) isoquinolinilo, quinolinilo o en especial indolilo, cada uno de los cuales está insustituido o sustituido como se describe anteriormente para hetero-ciclilo insustituido o sustituido, por ejemplo por uno a tres sustituyentes independientemente seleccionados a partir de halógeno, hidroxi, tal como cloro, alquilo de 1 a 7 átomos de carbono, tal como metilo, ciano y alcanoílo de 1 a 7 átomos de carbono, tal como acetilo; a partir de cicloalquilo mono- o bi-cíclico insustituido o sustituido como se describe anteriormente, en especial ciclopropilo, ciclobutilo, ciclo-pentilo, o ciclohexilo, cada uno de los cuales está insustituido o sustituido como se describe más adelante para cicloalquilo insustituido o sustituido; o en especial a partir del grupo que consiste en alquenilo de 2 a 7 átomos de carbono, alquinilo de 2 a 7 átomos de carbono, halógeno, hidroxi, alcoxilo de 1 a 7 átomos de carbono, halo-alcoxilo de 1 a 7 átomos de carbono, tal como trifluoro-metoxilo, hidroxi-alcoxilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono, fenil- o naftil-oxilo, fenil- o naftil-

alquiloxilo de 1 a 7 átomos de carbono, alcanoiloxilo de 1 a 7 átomos de carbono, (alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, fenil y/o fenil-alquilo de 1 a 7 átomos de carbono)-amino-carboniloxilo, benzoil- o naftoil-oxilo, tioalquilo de 1 a 7 átomos de carbono, halo-tioalquilo de 1 a 7 átomos de carbono, tal como trifluoro-tiometilo, hidroxi-tioalquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-tioalquilo de 1 a 7 átomos de carbono, tiofenilo o tionaftilo, fenil- o naftil-tioalquilo de 1 a 7 átomos de carbono, nitro, amino, mono- o di-(alquilo de 1 a 7 átomos de carbono, fenilo, naftilo, fenil-alquilo de 1 a 7 átomos de carbono, naftil-alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, y/o alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono)-amino, alcanoílo de 1 a 7 átomos de carbono-amino ****, benzoil- o naftoil-amino**--**, alquilo de 1 a 7 átomos de carbono-sulfonil-amino, fenil- o naftil-sulfonil-amino), fenil- o naftil-alquilo de 1 a 7 átomos de carbono-sulfonil-amino, fenil- o naftil-alquilo de 1 a 7 átomos de carbono-carbonil-amino, carboxilo, alquilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, fenil- o naftil-oxicarbonilo, fenil- o naftil-alcoxilo de 1 a 7 átomos de carbono-carbonilo, carbamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, N-mono- o N,N-di-(naftil- o fenil-alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, ciano,

sulfenilo (-S-OH), sulfonilo (-S(=O)-OH), alquilo de 1 a 7 átomos de carbono-sulfinilo (alquilo de 1 a 7 átomos de carbono-S(=O)-), fenil- o naftil-sulfinilo, fenil- o naftil-alquilo de 1 a 7 átomos de carbono-sulfinilo, sulfonilo, alquilo de 1 a 7 átomos de carbono-sulfonilo, fenil- o naftil-sulfonilo, fenil- o naftil-alquilo de 1 a 7 átomos de carbono-sulfonilo, sulfamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, fenil, naftil, fenil-alquilo de 1 a 7 átomos de carbono, o naftil-alquilo de 1 a 7 átomos de carbono)-amino-sulfonilo, N-mono-, N'-mono-, N,N-di-, o N,N,N'-tri-(alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, fenil y/o fenil-alquilo de 1 a 7 átomos de carbono)-amino-carbonil-amino o -amino-carboniloxilo, y N-mono-, N'-mono-, N,N-di-, o N,N,N'-tri-(alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, y/o alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono)-amino-sulfonil-amino;

en donde cualquier fenilo o naftilo mencionado como sustituyente de, o como parte de un sustituyente de arilo sustituido, está insustituido o sustituido por una o más, de preferencia hasta tres fracciones independientemente seleccionadas a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono, alquenilo de 1 a 7 átomos de carbono, alquinilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, tal como trifluoro-metilo, halógeno, en especial flúor,

cloro, bromo o yodo, hidroxi, alcoxilo de 1 a 7 átomos de carbono, feniloxilo, naftiloxilo, fenil- o naftil-alcoxilo de 1 a 7 átomos de carbono, alcanoiloxilo de 1 a 7 átomos de carbono, fenil- o naftil-alcanoiloxilo de 1 a 7 átomos de carbono, amino, mono- o di-(alquilo de 1 a 7 átomos de carbono, fenil, naftil, fenil-alquilo de 1 a 7 átomos de carbono, naftil-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono, y/o fenil- o naftil-alcanoílo de 1 a 7 átomos de carbono)-amino, carboxilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, fenoxi-carbonilo, naftiloxi-carbonilo, fenil-alquiloxilo de 1 a 7 átomos de carbono-carbonilo, naftil-alcoxilo de 1 a 7 átomos de carbono-carbonilo, carbamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, fenil, naftil, fenil-alquilo de 1 a 7 átomos de carbono, y/o naftil-alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, ciano, sulfo, sulfamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, fenil, naftil, fenil-alquilo de 1 a 7 átomos de carbono, y/o naftil-alquilo de 1 a 7 átomos de carbono)-amino-sulfonilo, y nitro, o de preferencia, en donde se mencionan los sustituyentes preferidos, por uno o más de estos sustituyentes mencionados.

Alquenilo insustituido o sustituido es de preferencia alquenilo de 2 a 20 átomos de carbono, más preferiblemente alquenilo de 2 a 7 átomos de carbono con uno o, si es posible, más dobles enlaces, que es de cadena recta o ramificada (una o, donde sea apropiado, más veces), el cual está insustituido o sustituido por una o más, por ejemplo hasta tres fracciones

seleccionadas a partir de aquéllas mencionadas como sustituyentes para alquilo sustituido, y a partir de arilo mono- o bi-cíclico insustituido o sustituido, cada uno de preferencia como se describe anteriormente. Los sustituyentes con un hidrógeno activo (por ejemplo, hidroxi o amino) de preferencia están presentes en la forma de tautómeros en equilibrio si están directamente enlazados a un átomo de carbono con un doble enlace, de preferencia en las posiciones en las que se eviten los sustituyentes con hidrógeno activo.

Alquinilo insustituido o sustituido es de preferencia alquinilo de 2 a 20 átomos de carbono, más preferiblemente alquinilo de 2 a 7 átomos de carbono con uno o, si es posible, más triples enlaces, que es de cadena recta o ramificada (una o, donde sea apropiado, más veces), el cual está insustituido o sustituido por una o más, por ejemplo hasta tres fracciones seleccionadas a partir de aquéllas mencionadas como sustituyentes para alquilo sustituido, y a partir de arilo mono- o bi-cíclico insustituido o sustituido, cada uno de preferencia como se describe anteriormente. Los sustituyentes con un hidrógeno activo (por ejemplo, hidroxi o amino) de preferencia están presentes en la forma de tautómeros en equilibrio si están directamente enlazados a un átomo de carbono con un triple enlace, de preferencia en las posiciones en las que se eviten los sustituyentes con hidrógeno activo.

Hidroxi esterificado es de preferencia aciloxilo, con acilo como se define en lo anterior, más preferiblemente alcanoiloxilo de

1 a 7 átomos de carbono o benzoiloxilo.

Hidroxi eterificado es de preferencia alquiloxilo de 1 a 7 átomos de carbono sustituido, en donde el alquilo sustituido es de preferencia como se define anteriormente, ariloxilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, heterocicliloxilo mono- o bi-cíclico insustituido o sustituido, heterocicliloxilo mono- o bi-cíclico-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, cicloalquiloxilo mono- o bi-cíclico insustituido o sustituido, o cicloalquilo mono- o bi-cíclico-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido (en donde, en cada caso, las fracciones de preferencia son como se definen anteriormente) o más preferiblemente alquiloxilo insustituido, en especial alquiloxilo de 1 a 7 átomos de carbono.

En donde un asterisco (*) marca el enlace que enlaza una fracción, y el enlace correspondiente es el que se muestra en la Fórmula correspondiente del compuesto respectivo de la Fórmula I (o un precursor del mismo) que enlaza a la fracción respectiva.

Las anteriores y en especial las siguientes modalidades preferidas de las fracciones y símbolos de la Fórmula I se pueden emplear independientemente unas de otras para reemplazar definiciones más generales y, por lo tanto, para definir las modalidades especialmente preferidas de la invención, en donde las definiciones restantes se pueden mantener amplias como se definen en las modalidades de las invenciones definidas

anteriormente o más adelante.

De una manera preferible, no más de uno de R_1 y R_2 es acilo, y el otro tiene uno de los significados dados anteriormente en la presente o más adelante en la presente para estas fracciones, diferente de acilo.

Como R^3, se prefieren en especial las fracciones de las fórmulas (a), (b), (c), (f), y ligeramente menos (g), más preferiblemente de las fórmulas (a), (b), ó (f).

El símbolo m de preferencia significa 0 ó 2.

R_d es de preferencia alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, o (si m = 2) es $-N(R_b)(R_c)$, en donde R_b y R_c son como se definen anteriormente o más adelante.

R_e es de preferencia hidrógeno.

De preferencia, cuando menos uno de R^4 y R^5 es hidrógeno (es decir, los compuestos preferidos de la invención son pirrolidinas (3,4-di-, 3,3-tri-, 3,4,4-tri-)-sustituidas), más preferiblemente ambos son hidrógeno.

En todas las definiciones anteriores y siguientes, la persona que tenga experiencia en la materia, sin una indebida experimentación o consideración, será capaz de reconocer las que

sean pertinentes (por ejemplo, aquéllas que, si están presentes, proporcionan compuestos que son suficientemente estables para la fabricación de productos farmacéuticos, por ejemplo, que tienen una vida de anaquel de más de 30 segundos), y por lo tanto, de preferencia son abarcadas por las presentes reivindicaciones, y que solamente son abarcados los enlaces y sustituciones químicamente factibles (por ejemplo, en el caso de los dobles o triples enlaces, los grupos amino o hidroxi que llevan hidrógeno y similares), así como las formas tautoméricas cuando estén presentes, en especial en equilibrio. Por ejemplo, de preferencia, por razones de estabilidad o factibilidad química, los átomos directamente vicinales en las cadenas de preferencia no son seleccionados a partir de oxi más oxi, tio más oxi, oxi más tio, o tio más tio, excepto en donde estén presentes sistemas de anillo o similares que sean suficientemente estables. Los sustituyentes que se enlazan por medio de un O (por ejemplo, en alcoxilo de 1 a 7 átomos de carbono) o S que sea parte de ellos, de preferencia no se enlazan al nitrógeno, por ejemplo en los anillos.

Las sales son en especial las sales farmacéuticamente aceptables de los compuestos de la Fórmula I. Se pueden formar en donde estén presentes grupos formadores de sales, tales como grupos básicos o ácidos, que puedan existir en una forma disociada cuando menos parcialmente, por ejemplo, en un intervalo de pH de 4 a 10 en soluciones acuosas, o se pueden aislar en especial en una forma sólida, especialmente cristalina.

Estas sales se forman, por ejemplo, como sales de adición de ácido, de preferencia con ácidos orgánicos o inorgánicos, a partir de los compuestos de la Fórmula I con un átomo de nitrógeno básico (por ejemplo, imino o amino), en especial las sales farmacéuticamente aceptables. Los ácidos inorgánicos adecuados son, por ejemplo, ácidos de halógeno, tales como ácido clorhídrico, ácido sulfúrico, o ácido fosfórico. Los ácidos orgánicos adecuados son, por ejemplo, los ácidos carboxílicos, fosfónicos, sulfónicos o sulfámicos, por ejemplo ácido acético, ácido propiónico, ácido láctico, ácido fumárico, ácido succínico, ácido cítrico, aminoácidos, tales como ácido glutámico o ácido aspártico, ácido maleico, ácido hidroxi-maleico, ácido metil-maleico, ácido benzoico, ácido metan- o etan-sulfónico, ácido etan-1,2-disulfónico, ácido bencen-sulfónico, ácido 2-naftalen-sulfónico, ácido 1,5-naftalen-disulfónico, ácido N-ciclohexil-sulfámico, ácido N-metil-, N-etil-, o N-propil-sulfámico, u otros ácidos protónicos orgánicos, tales como ácido ascórbico.

En la presencia de radicales negativamente cargados, tales como carboxilo o sulfo, también se pueden formar sales con bases, por ejemplo sales de metales o de amonio, tales como sales de metales alcalinos o de metales alcalinotérreos, por ejemplo sales de sodio, potasio, magnesio o calcio, o sales de amonio con amoníaco o con aminas orgánicas adecuadas, tales como monoaminas terciarias, por ejemplo trietil-amina o tri-(2-hidroxi-etil)-amina, o bases heterocíclicas, por ejemplo N-etil-piperidina o

N,N'-dimetil-piperazina.

Cuando están presentes un grupo básico y un grupo ácido en la misma molécula, un compuesto de la Fórmula I también puede formar sales internas.

Para propósitos de aislamiento o purificación, también es posible utilizar sales farmacéuticamente inaceptables, por ejemplo picratos o percloratos. Para uso terapéutico, solamente se emplean sales farmacéuticamente aceptables o los compuestos libres (cuando sea aplicable, comprendidos en preparaciones farmacéuticas), y por consiguiente, éstos son los preferidos.

En vista de la estrecha relación entre los compuestos en forma libre y en la forma de sus sales, incluyendo las sales que se pueden utilizar como intermediarios, por ejemplo en la purificación o identificación de los compuestos o sales de los mismos, cualquier referencia a "compuestos", "materiales de partida", e "intermediarios" anteriormente en la presente y más adelante en la presente, en especial a los compuestos de la Fórmula I o sus precursores, se debe entender que también se refiere a una o más sales de los mismos, o a una mezcla de un compuesto libre correspondiente y una o más sales del mismo, cada uno de los cuales pretende incluir también cualquier solvato, precursor metabólico tal como éster o amida del compuesto de la Fórmula I, o sal de cualquiera o más de los mismos, según sea apropiado y conveniente, y si no se menciona explícitamente de otra manera. Se pueden obtener diferentes formas de cristal, y entonces

también se incluyen.

Cuando se utiliza la forma plural para los compuestos, materiales de partida, intermediarios, sales, preparaciones farmacéuticas, enfermedades, trastornos, y similares, esto pretende significar uno (preferido) o más compuestos, sales, preparaciones farmacéuticas, enfermedades, trastornos individuales o similares, y cuando se utiliza el singular o el artículo indefinido ("un", "uno"), éste pretende incluir al plural (por ejemplo, también isómeros de diferente configuración del mismo compuesto, por ejemplo enantiómeros en racematos o similares), o de preferencia el singular ("uno").

Los compuestos de la presente invención pueden poseer dos o más centros asimétricos, dependiendo de la elección de los sustituyentes. Las configuraciones absolutas preferidas son como se indican específicamente en la presente. Sin embargo, la presente invención abarca cualesquiera posibles diaestereoisómeros aislados o puros, enantiómeros, o enantiómeros geométricos, y mezclas de los mismos, por ejemplo mezclas de enantiómeros, tales como racematos.

Como se describe anteriormente, la presente invención proporciona, en algunas de sus modalidades importantes, el uso de compuestos de pirrolidina (3,4-di-, 3,4,4-tri-, ó 3,3,4,4-tetra-)-sustituida para la preparación de una formulación farmacéutica para el tratamiento de una enfermedad que dependa de la actividad de la renina; el uso de un compuesto de esa clase en el

tratamiento de una enfermedad que dependa de la actividad de la renina; compuestos que son parte de una subclase de estos compuestos de pirrolidina sustituida para utilizarse en el diagnóstico y en el tratamiento terapéutico de un animal de sangre caliente, en especial para el tratamiento de una enfermedad (= trastorno) que dependa de la actividad de la renina; nuevos compuestos que son parte de una subclase de estos compuestos de pirrolidina sustituida; formulaciones farmacéuticas que comprenden a estos compuestos de pirrolidina sustituida, y/o un método de tratamiento que comprende administrar estos compuestos de pirrolidina sustituida, un método para la fabricación en especial de estos nuevos compuestos de pirrolidina sustituida, así como novedosos intermediarios, materiales de partida, y/o pasos parciales para su síntesis.

Una actividad "inapropiada" de la renina, de preferencia se refiere a un estado de un animal de sangre caliente, en especial un ser humano, en donde la renina muestra una actividad de renina que es demasiado alta en la situación dada (por ejemplo, debido a uno o más de mala regulación, sobre-expresión, por ejemplo debido a amplificación genética o a reconfiguración de cromosomas, o a infección por microorganismos, tales como virus que expresen un gen aberrante, actividad anormal, por ejemplo que conduzca a una especificidad de sustrato errónea, o una renina hiperactiva, por ejemplo producida en cantidades normales, una actividad demasiado baja de un producto con actividad de

renina que remueve sendas, una alta concentración de sustrato, y/o similares), y/o que conduzca a, o soporte, una enfermedad o trastorno dependiente de la renina como se menciona anteriormente y más adelante, por ejemplo por una actividad de renina demasiado alto. Esta actividad de renina inapropiada, por ejemplo, comprende una actividad más alta que la normal, o además una actividad en el intervalo normal o inclusive debajo del normal que, sin embargo, debido a procesos precedentes, paralelos, y/o subsecuentes, por ejemplo señalización, efecto regulador sobre otros procesos, más alta concentración de sustrato o de producto, y similares, conduzca a un soporte o mantenimiento directo o indirecto de la enfermedad o del trastorno, y/o una actividad que soporte el brote y/o la presencia de una enfermedad o trastorno de cualquier otra manera. La actividad inapropiada de la renina puede o no depender de otros mecanismos paralelos que soporten el trastorno o la enfermedad, y/o el efecto profiláctico o terapéutico puede o no incluir otros mecanismos en adición a la inhibición de la renina. Por consiguiente, "dependiente" se tiene que leer como "dependiente de, entre otras cosas" (especialmente en los casos en donde una enfermedad o trastorno sea en realidad exclusivamente dependiente sólo de la renina) de preferencia como "dependiente principalmente", y de una manera más preferible, como "dependiente esencialmente sólo de". Una enfermedad dependiente de una actividad (especialmente inapropiada) de la renina, también

puede ser una que simplemente responda a la modulación de la actividad de la renina, en especial que responda de una manera benéfica (por ejemplo, disminuyendo la presión sanguínea) en el caso de la inhibición de la renina.

Cuando se menciona una enfermedad o trastorno dependiente de la actividad inapropiada de una renina (tal como en la definición de "uso" en el siguiente párrafo, y también en especial cuando se menciona un compuesto de la Fórmula I para utilizarse en el diagnóstico o en el tratamiento terapéutico que de preferencia sea el tratamiento de una enfermedad o trastorno dependiente de una actividad inapropiada de la renina, esto se refiere de preferencia a cualquiera o más enfermedades o trastornos que dependan de una actividad inapropiada de la renina natural y/o de una o más formas alteradas o mutadas de la misma.

Cuando subsecuentemente o en lo anterior se menciona el término "uso" (como verbo o como nombre) (en relación con el uso de un compuesto de la Fórmula I o de una sal farmacéuticamente aceptable del mismo, o un método de uso del mismo), esto (si no se indica de una manera diferente, o para leerse de una manera diferente en el contexto) incluye cualquiera o más de las siguientes modalidades de la invención, respectivamente (si no se informa de otra manera): el uso en el tratamiento de una enfermedad o trastorno que dependa de una actividad (en especial inapropiada) de la renina, el uso para la fabricación de

composiciones farmacéuticas para utilizarse en el tratamiento de una enfermedad o trastorno que dependa de una actividad (especialmente inapropiada) de la renina; un método de uso de uno o más compuestos de la Fórmula I en el tratamiento de una enfermedad o trastorno que dependa de una actividad (especialmente inapropiada) de la renina; una preparación farmacéutica que comprenda uno o más compuestos de la Fórmula I para el tratamiento de una enfermedad o trastorno que dependa de una actividad (especialmente inapropiada) de la renina; y uno o más compuestos de la Fórmula I para utilizarse en el tratamiento de una enfermedad o trastorno en un animal de sangre caliente, en especial un ser humano, de preferencia una enfermedad que dependa de una actividad (especialmente inapropiada) de la renina; según sea apropiado y conveniente, si no se informa de otra manera.

Los términos "tratar", "tratamiento" o "terapia", se refieren al tratamiento profiláctico (por ejemplo, que demore o prevenga el establecimiento de una enfermedad o trastorno) o de preferencia terapéutico (incluyendo, pero no limitándose a, preventivo, demora del establecimiento y/o progreso, paliativo, curador, aliviador del síntoma, reductor del síntoma, aminorador de la condición del paciente, modulador de renina, y/o inhibidor de renina) de dichas enfermedades o trastornos, en especial de una o más enfermedades o trastornos mencionados anteriormente o más adelante.

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Modalidades Preferidas de Acuerdo con la Invención

Los grupos de modalidades preferidas de la invención mencionados en las reivindicaciones y más adelante, no deben considerarse como exclusivos, sino que más bien, por ejemplo, con el objeto de reemplazar las expresiones generales o símbolos con definiciones más específicas, las partes de estos grupos de compuestos se pueden intercambiar empleando las definiciones dadas anteriormente, o se pueden omitir, según sea apropiado, y cada una de las definiciones más específicas, independientemente de cualesquiera otras, se puede introducir de una manera independiente de, o junto con, una o más definiciones más específicas diferentes, para sustituir otras expresiones o símbolos más generales.

En una primera modalidad preferida, la invención se refiere a un compuesto de la Fórmula I en donde:

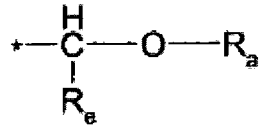
R^1 es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, alquenilo insustituido o sustituido, alquinilo sustituido o insustituido, o acilo;

R^2 es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico

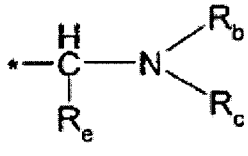
insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo monocíclico-alquilo sustituido o (de preferencia) arilo bicíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, alquenilo insustituido o sustituido, o alquinilo insustituido o sustituido; con la condición de que, si R^1 es una de las fracciones mencionadas en la definición de R^1 diferente de acilo, entonces R^2 también puede ser arilo monocíclico-alquilo insustituido (o sustituido) (significando que, en adición al grupo de otras fracciones mencionadas en la definición de R^2, el sustituyente R^2 también se puede seleccionar a partir de arilo monocíclico-alquilo insustituido);

R^3 es una fracción seleccionada a partir del grupo de fracciones de las fórmulas:

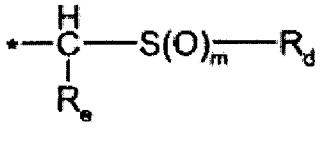
(a)



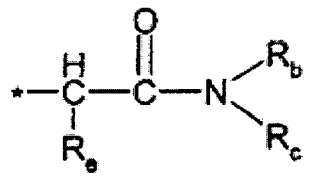
(b)



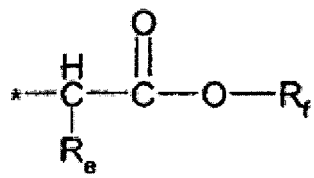
(c)



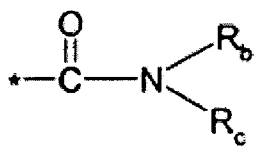
(d)



(e)

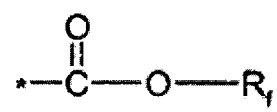


(f)



y

(g)



en donde, en cualquiera de las fracciones de las fórmulas dadas anteriormente bajo (a), (b), (c), (d), (e), (f), y (g), el asterisco (*) muestra el enlace que enlaza a la fracción R^3 respectiva con el resto de la molécula en la Fórmula I,

R_a es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, acilo, o hidrógeno;

R_b y R_c se seleccionan independientemente a partir del grupo que consiste en alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo bicíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, acilo, o hidrógeno, con la condición de que, de preferencia, no más de uno de R_b y R_c sea acilo, y con la condición de que, si R_c es una de las fracciones mencionadas diferente de acilo (significando aquí y posteriormente en la presente que R_c es una de las fracciones mencionadas para R_b y R_c excepto acilo, en especial R_c = hidrógeno o alquilo de 1 a 7 átomos de carbono), entonces R_b también puede ser (como una alternativa adicional a las otras fracciones mencionadas) arilo monocíclico-alquilo insustituido o sustituido;

R_d es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, o (de preferencia si **m** es 0) acilo, o puede tener uno de estos significados, o puede ser $-N(R_b(R_c)$ si **m** es 1 ó de preferencia 2;

R_e es hidrógeno, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, o alquilo de 1 a 7 átomos de carbono sustituido o de preferencia insustituido; y

R_f es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido;

m es 0, 1, ó 2;

cada uno de R^4 y R^5 se selecciona, independiente-mente uno del otro, a partir de hidrógeno, alquilo insustituido o sustituido, hidroxi, o hidroxi esterificado o eterificado;

y T es metileno ($-CH_2-$), metileno mono-sustituido por alquilo (-[C(H)(alquilo)]-), carbonilo (-C(=O)-) (preferido), o tio-carbonilo (-C(=S)-);

o una sal farmacéuticamente aceptable del mismo,

para utilizarse en el tratamiento (terapéutico o profiláctico) de un mamífero, en especial un ser humano, de preferencia de una enfermedad que dependa de la actividad de la renina, en especial una enfermedad que responsa a la inhibición de la renina de una manera benéfica, más preferiblemente hipertensión.

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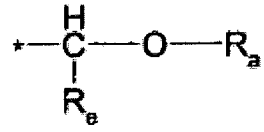
Con respecto a los nuevos compuestos, la invención especialmente, en una modalidad todavía más preferida, se refiere a un compuesto de la Fórmula I, en donde:

R^1 es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, alquenilo insustituido o sustituido, alquinilo sustituido o insustituido, o acilo;

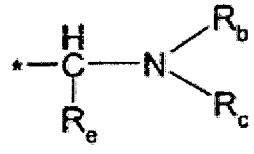
R^2 es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo bicíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, alquenilo insustituido o sustituido, o alquinilo insustituido o sustituido; con la condición de que, si R^1 es una de las fracciones mencionadas en la definición de R^1 diferente de acilo, entonces R^2 también puede ser arilo monocíclico-alquilo insustituido o sustituido (significando que, en adición al grupo de otras fracciones mencionadas en la definición de R^2, el sustituyente R^2 también se puede seleccionar a partir de arilo monocíclico-alquilo insustituido);

R^3 es una fracción seleccionada a partir del grupo de fracciones de las fórmulas:

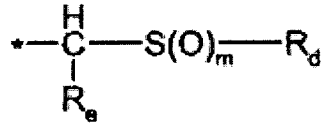
(a)



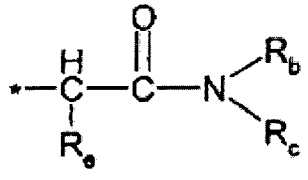
(b)



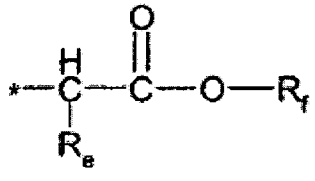
(c)



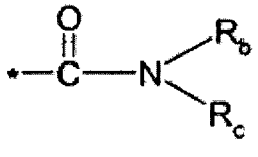
(d)



(e)

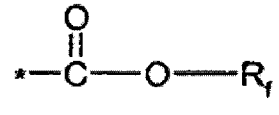


(f)



y

(g)



en donde, en cualquiera de las fracciones de las fórmulas dadas anteriormente bajo (a), (b), (c), (d), (e), (f), y (g), el asterisco (*) muestra el enlace que enlaza a la fracción R^3 respectiva con el resto de la molécula en la Fórmula I,

R_a es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, acilo, o hidrógeno;

R_b y R_c se seleccionan independientemente a partir del grupo que consiste en alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo bicíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, acilo, o hidrógeno, con la condición de que, de preferencia, no más de uno de R_b y R_c sea acilo, y con la condición de que, si R_c es una de las fracciones mencionadas diferente de acilo (en la definición de R_c en este párrafo), entonces R_b también puede ser arilo monocíclico-alquilo insustituido o sustituido;

R_d, en una fracción de las fórmulas (c) ó (e), es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o

sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, o (de preferencia si **m** es 0) acilo, o puede tener uno de estos significados, o puede ser -$N(R_b(R_c)$ si m es 1 ó de preferencia 2;

R_e es hidrógeno (preferido), arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, o alquilo de 1 a 7 átomos de carbono sustituido o de preferencia insustituido; y

R_f es alquilo sustituido o de preferencia arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido;

m es 0, 1, ó 2;

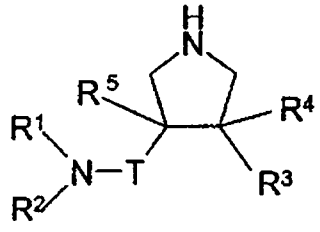
cada uno de R^4 y R^5 se selecciona, independiente-mente uno del otro, a partir de hidrógeno, alquilo insustituido o sustituido, hidroxi, o hidroxi esterificado o eterificado;

y T es metileno (-CH_2-) (preferido), metileno mono-sustituido por alquilo (-[C(H)(alquilo)]-), carbonilo (-C(=O)-)

(preferido), o tio-carbonilo (-C(=S)-);

o una sal (de preferencia farmacéuticamente aceptable) del mismo.

Un compuesto de la Fórmula I como tal:



(I)

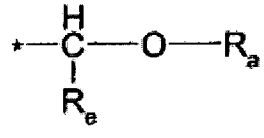
en donde:

R^1 es acilo;

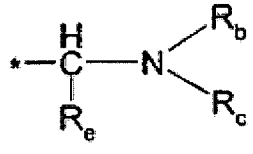
R^2 es alquilo insustituido o sustituido,

R^3 es una fracción seleccionada a partir del grupo de fracciones de las fórmulas:

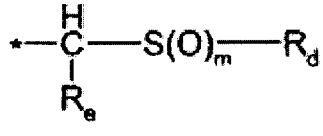
(a)



(b)

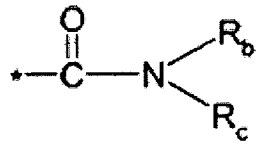


(c)



y

(f)



en donde, en cualquiera de las fracciones de las fórmulas dadas anteriormente bajo (a), (b), (c), y (f), el asterisco (*) muestra el enlace que enlaza a la fracción R^3 respectiva con el resto de la molécula en la Fórmula I, más preferiblemente seleccionada a partir de las fracciones de la Fórmula (a), (b), ó (f);

R_a es acilo o hidrógeno;

R_b es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, o acilo;

R_c es hidrógeno, hidroxi-alquilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, o de preferencia cicloalquilo de 3 a 8 átomos de carbono o alquilo de 1 a 7 átomos de carbono;

R_d es arilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, o $-N(R_b(R_c)$;

R_e es hidrógeno o alquilo de 1 a 7 átomos de carbono; y

m es 2;

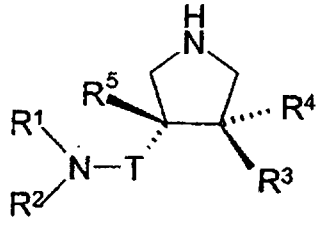
cada uno de R^4 y R^5 se selecciona, independiente-mente uno del otro, a partir de hidrógeno, alquilo insustituido o sustituido, hidroxi, o hidroxi esterificado o eterificado; en donde de preferencia cuando menos uno, más preferible-mente ambos de R^4 y R^5 son hidrógeno;

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y T es metileno (-CH_2-) (preferido), metileno mono-sustituido por alquilo (-[C(H)(alquilo)]-), carbonilo (-C(=O)-) (preferido), o tio-carbonilo (-C(=S)-);

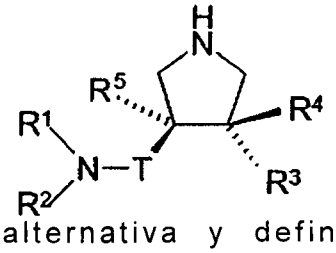
o una sal (en especial farmacéuticamente aceptable) del mismo, es una modalidad preferida adicional de la invención.

De una manera altamente preferible, un compuesto de la Fórmula I en las modalidades anteriores y siguientes (ya sea el uso, el compuesto para uso, o el nuevo compuesto) es de la Fórmula IA, con la siguiente configuración:



(IA)

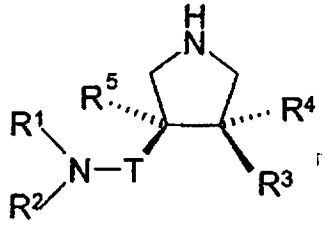
De una manera alternativa y definiendo una modalidad todavía preferida de la invención, un compuesto de la Fórmula I en las modalidades anteriores y siguientes (ya sea el uso, el compuesto para uso, o el nuevo compuesto) puede ser de la Fórmula IB, con la siguiente configuración:



(IB)

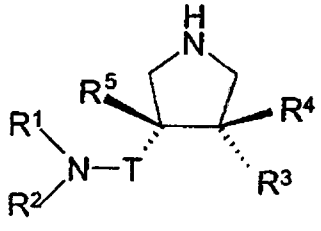
De una manera alternativa y definiendo una modalidad todavía preferida de la invención, un compuesto de la Fórmula I en

las modalidades anteriores y siguientes (ya sea el uso, el compuesto para uso, o el nuevo compuesto) puede ser de la Fórmula IC, con la siguiente configuración:



(IC)

De una manera alternativa y definiendo una modalidad todavía preferida de la invención, un compuesto de la Fórmula I en las modalidades anteriores y siguientes (ya sea el uso, el compuesto para uso, o el nuevo compuesto) puede ser de la Fórmula ID, con la siguiente configuración:



(ID)

En cada una de las fórmulas IA, IB, IC, y ID, las fracciones R^1, R^2, R^3, R^4, R^5, y L son como se definen anteriormente en la presente o de preferencia posteriormente en la presente para las modalidades más generales respectivas, o en especial más preferidas, de la invención.

Las fórmulas IA, IB, IC, ó ID pueden reemplazar a la Fórmula I siempre que se mencione más adelante en la presente o

posteriormente en la presente un compuesto de la Fórmula I (incluyendo una sal del mismo); también, se prefieren los intermediarios correspondientes.

Una modalidad preferida adicional de la invención se refiere al uso de un compuesto de la Fórmula I, en donde:

R^1 es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, alquenilo insustituido o sustituido, alquinilo sustituido o insustituido, o acilo;

R^2 es arilo mono- o bi-cíclico-alquilo insustituido o sustituido;

R^3 es una fracción seleccionada a partir del grupo de fracciones de las fórmulas (a), (b), (c), (d), (e), (f), ó (g), más preferiblemente de las fórmulas (a), (b), (c), y (f), todavía de una manera más preferible de las fórmulas (a), (b), ó (f), dadas en la primera descripción de un compuesto de la Fórmula I en esta divulgación; en donde, en cualquiera de las fracciones de las fórmulas de fracciones, el asterisco (*) muestra el enlace que enlaza a la fracción R^3 respectiva con el resto de la molécula en la Fórmula I,

R_a es alquilo insustituido o sustituido, arilo mono- o bi-

cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, acilo, o hidrógeno;

R_b y R_c se seleccionan independientemente a partir de las fracciones dadas en R_a, con la condición de que, de preferencia, no más de uno de R_b y R_c sea acilo;

R_d es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, o (de preferencia si m es 0) acilo, o puede tener uno de estos significados, o puede ser $-N(R_b(R_c)$ si m es 1 ó de preferencia 2;

R_e es arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, o alquilo de 1 a 7 átomos de carbono sustituido o de preferencia insustituido, o hidrógeno; y

R_f es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico

insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido;

m es 0, 1, ó 2, de preferencia 0, o de una manera más preferible 2;

cada uno de R^4 y R^5 se selecciona, independiente-mente uno del otro, a partir de hidrógeno, alquilo insustituido o sustituido, hidroxi, o hidroxi esterificado o eterificado;

y T es metileno ($-CH_2-$), metileno mono-sustituido por alquilo (-[C(H)(alquilo)]-), carbonilo (-C(=O)-), o tio-carbonilo (-C(=S)-);

o una sal farmacéuticamente aceptable del mismo,

en la preparación de una formulación farmacéutica para el tratamiento de una enfermedad que dependa de la actividad de la renina, en especial hipertensión; o en el tratamiento de una enfermedad que dependa de la actividad de la renina, en especial hipertensión.

Otra modalidad preferida de la invención se refiere al uso de un compuesto de la Fórmula I, en donde R^1 es fenilo, naftilo, heterociclilo mono- o bi-cíclico, fenil-carbonilo, fenil-acetilo, naftil-carbonilo, naftil-acetilo, heterociclilo mono- o bi-cíclico-carbonilo, o acetilo, fenil-sulfonilo, naftil-sulfonilo, o heterociclilo mono- o bi-cíclico-sulfonilo; en donde el heterociclilo mono- o bi-cíclico es

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pirrolilo, furanilo, tienilo (= tiofenilo), tiazolilo, pirazolilo, triazolilo, tetrazolilo, oxetidinilo, 3-(alquilo de 1 a 7 átomos de carbono)-oxetidinilo, piridilo, pirimidinilo, morfolino, tio-morfolino, piperidinilo, piperazinilo, pirrolidinilo, tetrahidro-furanilo, tetrahidro-furan-onilo, tetrahidro-piranilo, 1H-indazolilo, benzo-furanilo, benzo-tiofenilo, o de una manera más preferible, isoquinolilo, quinolilo, o en especial indolilo, y cada heterociclilo mono- o bi-cíclico, fenilo, o naftilo mencionados bajo R^1, está insustituido o de preferencia sustituido por una o más, en especial por una a tres fracciones, de preferencia independientemente seleccionadas a partir del grupo que consiste en:

(i) un sustituyente de la Fórmula -(alquileno de 0 a 7 átomos de carbono)-$(X)_r$-(alquileno de 1 a 7 átomos de carbono)-$(Y)_s$-(alquileno de 0 a 7 átomos de carbono)-H (en especial en arilo sustituido o aril-alquilo sustituido como R^1), en donde alquileno de 0 átomos de carbono significa que está presente un enlace en lugar de alquileno enlazado, y alquileno en cada caso puede ser de cadena recta o ramificada, y puede estar insustituido o (con menor preferencia) sustituido, por ejemplo, por una o más fracciones como se definen para alquilo sustituido, en especial por halógeno, especialmente flúor, hidroxi, alcoxilo de 1 a 7 átomos de carbono, feniloxilo, naftiloxilo, alcanoiloxilo de 1 a 7 átomos de carbono, benzoiloxilo, naftoiloxilo, amino, mono- o di-(alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono, fenil-alcanoílo de 1 a 7 átomos de carbono, naftil-alcanoílo de 1 a

7 átomos de carbono, fenilo, naftilo, fenil-alquilo de 1 a 7 átomos de carbono, y/o naftil-alquilo de 1 a 7 átomos de carbono)-amino, carboxilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, o ciano; r y s, cada uno independiente-mente del otro, son 0 ó 1, y cada uno de X e Y, si están presentes e independientemente de los otros, es -O-, -NV-, -S-, -O-CO-, -CO-O-, -NV-CO-; -CO-NV-; -NV-SO_2-; -SO_2-NV; -NV-CO-NV-, -NV-CO-O-, -O-CO-NV-, -NV-SO_2-NV-, en donde V es hidrógeno o alquilo insustituido o sustituido como se define más adelante, en especial alquilo de 1 a 7 átomos de carbono, o es fenilo, naftilo, fenil- o naftil-alquilo de 1 a 7 átomos de carbono, o halo-alquilo de 1 a 7 átomos de carbono; por ejemplo, alquilo de 1 a 7 átomos de carbono, tal como metilo, etilo, propilo normal, isopropilo, butilo normal, isobutilo, butilo secundario, o butilo terciario, halo-alquilo de 1 a 7 átomos de carbono, tal como trifluorometilo, hidroxi-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, tal como 3-metoxi-propilo ó 2-metoxi-etilo, alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, feniloxi- o naftiloxi-alquilo de 1 a 7 átomos de carbono, alcanoiloxilo de 1 a 7 átomos de carbono- alquilo de 1 a 7 átomos de carbono, amino-alquilo de 1 a 7 átomos de carbono, tal como amino-metilo, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-amino-alquilo de 1 a 7 átomos de carbono, mono- o di- (alquilo de 1 a 7 átomos de carbono, naftil, fenil, naftil-alquilo de 1 a 7 átomos de

carbono, y/o fenil-alquilo de 1 a 7 átomos de carbono)-amino-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono-amino-alquilo de 1 a 7 átomos de carbono, alquilo de 1 a 7 átomos de carbono-O-CO-NH-alquilo de 1 a 7 átomos de carbono, alquilo de 1 a 7 átomos de carbono-sulfonil-amino-alquilo de 1 a 7 átomos de carbono, alquilo de 1 a 7 átomos de carbono-NH-CO-NH-alquilo de 1 a 7 átomos de carbono, alquilo de 1 a 7 átomos de carbono-NH-SO_2-NH-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono, hidroxi-alcoxilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono, alcanoiloxilo de 1 a 7 átomos de carbono, halo-alcoxilo de 1 a 7 átomos de carbono, tal como fluoro-metoxilo, fenil- o naftil-alcanoiloxilo de 1 a 7 átomos de carbono, fenil- o naftil-alquilo de 1 a 7 átomos de carbono-amino-carboniloxilo, halo-tioalquilo de 1 a 7 átomos de carbono, tal como trifluoro-tiometilo, fenil- o naftil-tioalquilo de 1 a 7 átomos de carbono, mono- o di-(alquilo de 1 a 7 átomos de carbono-, naftil-alquilo de 1 a 7 átomos de carbono-, fenil-alquilo de 1 a 7 átomos de carbono-, y/o alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-)amino, alcanoílo de 1 a 7 átomos de carbono-amino, alquilo de 1 a 7 átomos de carbono-sulfonil-amino, fenil- o naftil-alcanoílo de 1 a 7 átomos de carbono-amino, fenil- o naftil-alquilo de 1 a 7 átomos de carbono-amino-carbonil-amino, carboxi-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-carbonilo, hidroxi-alcoxilo de 1 a 7 átomos de

carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono-carbonilo, amino-alcoxilo de 1 a 7 átomos de carbono-carbonilo, (N-) mono-(alquilo de 1 a 7 átomos de carbono)-amino-alcoxilo de 1 a 7 átomos de carbono-carbonilo, alcanoílo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono-carbonilo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, naftil-alquilo de 1 a 7 átomos de carbono, y/o fenil-alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, alquilo de 1 a 7 átomos de carbono-sulfonilo, halo-alquilo de 1 a 7 átomos de carbono-sulfonilo, hidroxi-alquilo de 1 a 7 átomos de carbono-sulfonilo, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-sulfonilo, amino-alquilo de 1 a 7 átomos de carbono-sulfonilo, N-mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino-alquilo de 1 a 7 átomos de carbono-sulfonilo, alcanoílo de 1 a 7 átomos de carbono-amino-alquilo de 1 a 7 átomos de carbono-sulfonilo, N-alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-carbamoílo, o N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino-sulfonilo;

(ii) a partir de alquenilo de 2 a 7 átomos de carbono, alquinilo de 2 a 7 átomos de carbono, fenilo, naftilo, hetero-ciclilo mono- o bi-cíclico, en especial como se define más adelante para heterociclilo mono- o bi-cíclico, de preferencia seleccionado a partir de pirrolilo, furanilo, tienilo, pirimidin-2,4-dion-1-, -3-, ó -5-ilo. tetrahidro-piranilo y tetrahidro-furanilo, fenil- o naftil-, o (heterociclilo mono- o bi-cíclico)-alquilo de 1 a 7 átomos de

carbono o alquiloxilo de 1 a 7 átomos de carbono, en donde heterociclilo mono- o bi-cíclico es como se define más adelante, de preferencia seleccionado a partir de pirrolilo, furanilo, tetrahidrofuranilo, tetrahidropiranilo, y tienilo; tal como bencilo o naftil-metilo, tetrahidro-furanil- o tetrahidro-piranil-alquiloxilo de 1 a 7 átomos de carbono-carbonilo, benzoil- o naftoil-amino-alquilo de 1 a 7 átomos de carbono, (fenil- o naftil- o heterociclilo mono- o bi-cíclico)-sulfonil-amino-alquilo de 1 a 7 átomos de carbono, en donde fenilo o naftilo o heterociclilo mono- o bi-cíclico está insustituido o sustituido, de preferencia por una o más, en especial por una a tres fracciones de alquilo de 1 a 7 átomos de carbono, (fenil o naftil o heterociclilo mono- o bi-cíclico)-alquilo de 1 a 7 átomos de carbono-sulfonil-amino-alquilo de 1 a 7 átomos de carbono, halógeno, hidroxi, fenil-alcoxilo de 1 a 7 átomos de carbono en donde el fenilo está de preferencia insustituido o sustituido, de preferencia por alcoxilo de 1 a 7 átomos de carbono y/o halógeno, heterociclilo mono- o bi-cíclico-alcoxilo de 1 a 7 átomos de carbono, (heterociclilo mono- o bi-cíclico o fenil o naftil)-oxilo, naftil-alquiloxilo de 1 a 7 átomos de carbono, (benzoil o naftoil o heterociclilo mono- o bi-cíclico-carbonil)-oxilo, (fenil o naftil o hetero-ciclilo mono- o bi-cíclico)-amino-carboniloxilo, (fenil o naftil o heterociclilo mono- o bi-cíclico)-tio, (benzoil o naftoil o heterociclilo mono- o bi-cíclico)-tio, nitro, amino, di-((naftil o fenil o heterociclilo mono- o bi-cíclico)-alquilo de 1 a 7 átomos de carbono)-amino, (benzoil o naftoil o heterociclilo mono- o bi-

cíclico)-amino, (fenil o naftil o heterociclilo mono- o bi-cíclico)-sulfonil-amino, en donde el fenilo o naftilo está insustituido o sustituido, de preferencia por una o más, en especial por una a tres fracciones de alquilo de 1 a 7 átomos de carbono, (fenil o naftil o heterociclilo mono- o bi-cíclico)-alquilo de 1 a 7 átomos de carbono-sulfonil-amino, (fenil o naftil o heterociclilo mono- o bi-cíclico)-amino-carbonil-amino, (fenil o naftil o heterociclilo mono- o bi-cíclico)-oxicarbonil-amino, (fenil o naftil o heterociclilo mono- o bi-cíclico)-alquiloxilo de 1 a 7 átomos de carbono-carbonil-amino, carboxilo, alquilo de 1 a 7 átomos de carbono-carbonilo, halo-alquilo de 1 a 7 átomos de carbono-carbonilo, hidroxi-alquilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-carbonilo, amino-alquilo de 1 a 7 átomos de carbono-carbonilo, (N-) mono- o (N,N-) di-(alquilo de 1 a 7 átomos de carbono)-amino-alquilo de 1 a 7 átomos de carbono-carbonilo, alcanoílo de 1 a 7 átomos de carbono-amino-alquilo de 1 a 7 átomos de carbono-carbonilo, halo-alcoxilo de 1 a 7 átomos de carbono-carbonilo, (fenil o naftil o heterociclilo mono- o bi-cíclico)-oxi-carbonilo, (fenil o naftil o heterociclilo mono- o bi-cíclico)-alcoxilo de 1 a 7 átomos de carbono-carbonilo, (N,N-) di-(alquilo de 1 a 7 átomos de carbono)-amino-alcoxilo de 1 a 7 átomos de carbono-carbonilo, carbamoílo, N-mono- o N,N-di-(naftil o fenil o heterociclilo mono- o bi-cíclico)-amino-carbonilo, ciano, alquileno de 1 a 7 átomos de carbono que está insustituido o sustituido por hasta cuatro sustituyentes de

alquilo de 1 a 7 átomos de carbono, y enlazado a dos átomos adyacentes del anillo de la fracción de arilo, sulfenilo, sulfinilo, alquilo de 1 a 7 átomos de carbono-sulfinilo, (fenil o naftil o heterociclilo mono- o bi-cíclico)-sulfinilo en donde el fenilo o naftilo está insustituido o sustituido de preferencia por una o más, en especial por una a tres fracciones de alquilo de 1 a 7 átomos de carbono, fenil- o naftil-alquilo de 1 a 7 átomos de carbono-sulfinilo, sulfonilo, (fenil o naftil o heterociclilo mono- o bi-cíclico)-sulfonilo en donde el fenilo o naftilo está insustituido o sustituido de preferencia por una o más, en especial por una a tres fracciones de alquilo de 1 a 7 átomos de carbono, (fenil o naftil o heterociclilo mono- o bi-cíclico)-alquilo de 1 a 7 átomos de carbono-sulfonilo, sulfamoílo, y N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, fenil, naftil, heterociclilo mono- o bi-cíclico, fenil-alquilo de 1 a 7 átomos de carbono, naftil-alquilo de 1 a 7 átomos de carbono, y/o heterociclilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono)-amino-sulfonilo;

en donde cualquier fenilo o naftilo o heterociclilo mono- o bi-cíclico - cuyo heterociclilo mono- o bi-cíclico de preferencia es como se define para heterociclilo mono- o bi-cíclico, más preferiblemente se selecciona a partir de pirrolilo, furanilo, tetrahidrofuranilo, tetrahidropiranilo, y tienilo - mencionado como sustituyente de, o como parte de un sustituyente de heterociclilo mono- o bi-cíclico, fenilo o naftilo R^1 bajo (i) ó (ii) está insustituido o sustituido por una o más, de preferencia hasta tres fracciones

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independientemente seleccionadas a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono, alquenilo de 1 a 7 átomos de carbono, alquinilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, tal como trifluoro-metilo, halógeno, en especial flúor, cloro, bromo o yodo, hidroxi, alcoxilo de 1 a 7 átomos de carbono, feniloxilo, naftiloxilo, fenil- o naftil-alcoxilo de 1 a 7 átomos de carbono, alcanoiloxilo de 1 a 7 átomos de carbono, fenil- o naftil-alcanoiloxilo de 1 a 7 átomos de carbono, amino, mono- o di-(alquilo de 1 a 7 átomos de carbono, fenil, naftil, fenil-alquilo de 1 a 7 átomos de carbono, naftil-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono, y/o fenil- o naftil-alcanoílo de 1 a 7 átomos de carbono)-amino, carboxilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, fenoxi-carbonilo, naftiloxi-carbonilo, fenil-alquiloxilo de 1 a 7 átomos de carbono-carbonilo, naftil-alcoxilo de 1 a 7 átomos de carbono-carbonilo, carbamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, fenil, naftil, fenil-alquilo de 1 a 7 átomos de carbono, y/o naftil-alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, ciano, sulfo, sulfamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, fenil, naftil, fenil-alquilo de 1 a 7 átomos de carbono, y/o naftil-alquilo de 1 a 7 átomos de carbono)-amino-sulfonilo, y nitro, o de preferencia, en donde se mencionan los sustituyentes preferidos, por uno o más de estos sustituyentes mencionados;

R^2 es fenilo, naftilo, fenil-alquilo de 1 a 7 átomos de carbono, o naftil-alquilo de 1 a 7 átomos de carbono, en donde

cada fenilo o naftilo mencionados hasta ahora en la definición de R^2 está insustituido o sustituido como justamente se describió para fenilo o naftilo sustituido en la definición de R^1,

o es de preferencia alquilo de 1 a 7 átomos de carbono que está insustituido o sustituido por uno o más, en especial hasta tres, por ejemplo uno o dos sustituyentes independientemente seleccionados a partir del grupo que consiste en alquenilo de 2 a 7 átomos de carbono, alquinilo de 2 a 7 átomos de carbono, halógeno, hidroxi, alcoxilo de 1 a 7 átomos de carbono, halo-alcoxilo de 1 a 7 átomos de carbono, tal como trifluoro-metoxilo, hidroxi-alcoxilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono, fenil- o naftil-oxilo, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono, alcanoiloxilo de 1 a 7 átomos de carbono, (alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, fenilo, y/o fenil-alquilo de 1 a 7 átomos de carbono)-amino-carboniloxilo, benzoil- o naftoil-oxilo, tioalquilo de 1 a 7 átomos de carbono, halo-tioalquilo de 1 a 7 átomos de carbono, tal como trifluoro-tiometilo, hidroxi-tioalquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-tioalquilo de 1 a 7 átomos de carbono, tiofenilo o tionaftilo, fenil- o naftil-tioalquilo de 1 a 7 átomos de carbono, nitro, amino, mono- o di-(alquilo de 1 a 7 átomos de carbono, fenilo, naftilo, fenil-alquilo de 1 a 7 átomos de carbono, naftil-alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo

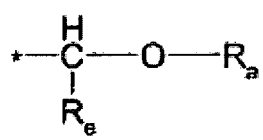
de 1 a 7 átomos de carbono, y/o alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono)-amino, alcanoílo de 1 a 7 átomos de carbono-amino, benzoil- o naftoil-amino, fenil- o naftil-alquilo de 1 a 7 átomos de carbono-carbonil-amino, alquilo de 1 a 7 átomos de carbono-sulfonil-amino, fenil- o naftil-sulfonil-amino, en donde el fenilo o naftilo está insustituido o sustituido por una o más, en especial por una a tres fracciones de alquilo de 1 a 7 átomos de carbono, fenil- o naftil-alquilo de 1 a 7 átomos de carbono-sulfonil-amino, carboxilo, alquilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, fenil- o naftil-oxicarbonilo, fenil- o naftil-alcoxilo de 1 a 7 átomos de carbono-carbonilo, carbamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, N-mono- o N,N-di-(naftil- o fenil-alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, ciano, sulfenilo (-S-OH), sulfonilo (-S(=O)-OH), alquilo de 1 a 7 átomos de carbono-sulfinilo (alquilo de 1 a 7 átomos de carbono-S(=O)-), fenil- o naftil-sulfinilo, en donde fenilo o naftilo está insustituido o sustituido por una o más, en especial por una a tres fracciones de alquilo de 1 a 7 átomos de carbono, fenil- o naftil-alquilo de 1 a 7 átomos de carbono-sulfinilo, sulfonilo, alquilo de 1 a 7 átomos de carbono-sulfonilo, fenil- o naftil-sulfonilo, en donde el fenilo o naftilo está insustituido o sustituido por una o más, en especial por una a tres fracciones de alquilo de 1 a 7 átomos de carbono, fenil- o naftil-alquilo de 1 a 7 átomos de carbono-sulfonilo, sulfamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, fenilo,

naftilo, fenil-alquilo de 1 a 7 átomos de carbono, o naftil-alquilo de 1 a 7 átomos de carbono)-amino-sulfonilo, N-mono-, N'-mono-, N,N-di-, ó N,N,N'-tri-(alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, fenilo, y/o fenil-alquilo de 1 a 7 átomos de carbono)-amino-carbonil-amino o -amino-carboniloxilo, y N-mono-, N'-mono-, N,N-di-, ó N,N,N'-tri-(alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, y/o alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono)-amino-sulfonil-amino;

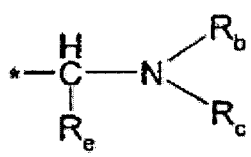
o cicloalquilo de 3 a 10 átomos de carbono, o ciclo-alquilo de 3 a 10 átomos de carbono-alquilo de 1 a 7 átomos de carbono;

R^3 es una fracción seleccionada a partir del grupo de fracciones de las fórmulas:

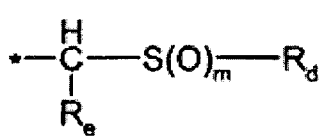
(a)



(b)

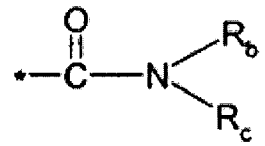


(c)



y

(f)



en donde, en cualquiera de las fracciones de las fórmulas dadas anteriormente bajo (a), (b), (c), y (f), el asterisco (*) muestra el enlace que enlaza a la fracción R^3 respectiva con el resto de la molécula en la Fórmula I;

R_a es acilo seleccionado a partir del grupo que consiste en alcanoílo de 1 a 7 átomos de carbono, tal como acetilo, 3,3-dimetil-butirilo, 2,2-dimetil-propionilo, ó 3,3-dimetil-butirilo, fenil-alcanoílo de 1 a 7 átomos de carbono insustituido (o con menor preferencia) mono-, di-, o tri-sustituido por (halo-alcoxilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono-alquiloxilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, y/o alquilo de 1 a 7 átomos de carbono), cicloalquilo de 3 a 8 átomos de carbono-carbonilo, o cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono-carbonilo, tal como ciclopropil-carbonilo, ciclobutil-carbonilo, ciclohexil-acetilo, o ciclo-hexil-carbonilo, (tetrahidro-furanil o tetrahidro-piranil)-carbonilo, o (tetrahidrofuranil o tetrahidropiranil)-alquilo de 1 a 7 átomos de carbono-carbonilo, tal como tetrahidro-furanil-carbonilo, tetrahidro-piranil-carbonilo, tetrahidro-furanil-acetilo, o tetrahidro-piranil-acetilo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-

amino-carbonilo, N-[fenil, o fenil-alquilo de 1 a 7 átomos de carbono (por ejemplo, bencilo)]-amino-carbonilo, N-[cicloalquilo de 3 a 8 átomos de carbono (por ejemplo, ciclohexilo-) o cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono]-amino-carbonilo, alquilo de 1 a 7 átomos de carbono-amino-carbonilo, o (alquilo de 1 a 7 átomos de carbono, fenilo, naftilo, fenil-alquilo de 1 a 7 átomos de carbono, y/o naftil-alquilo de 1 a 7 átomos de carbono)-oxicarbonilo, por ejemplo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, tal como terbutiloxi-carbonilo o isobutiloxi-carbonilo, o fenil-alquiloxilo de 1 a 7 átomos de carbono-carbonilo; o es hidrógeno;

R_b es alquilo de 1 a 7 átomos de carbono o fenilo, naftilo, fenil-alquilo de 1 a 7 átomos de carbono, o naftil-alquilo de 1 a 7 átomos de carbono - en cada caso insustituido o sustituido -, en donde, en el caso de una fracción sustituida, los sustituyentes son uno o más, en especial hasta tres sustituyentes independientemente seleccionados a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono, tal como metilo, etilo, propilo normal, isopropilo, butilo normal, isobutilo, butilo secundario o butilo terciario, alquenilo de 2 a 7 átomos de carbono, alquinilo de 2 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, tal como trifluoro-metilo, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, tal como 3-metoxi-propilo ó 2-metoxi-etilo, amino-alquilo de 1 a 7 átomos de carbono, alcoxilo de

1 a 7 átomos de carbono, hidroxi-alcoxilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono, alcanoiloxilo de 1 a 7 átomos de carbono, amino, mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino, alcanoílo de 1 a 7 átomos de carbono-amino, alquilo de 1 a 7 átomos de carbono-sulfonil-amino, alcoxilo de 1 a 7 átomos de carbono-carbonilo, carboxi-alquilo de 1 a 7 átomos de carbono, halógeno, hidroxi, halo-alcoxilo de 1 a 7 átomos de carbono, tal como trifluoro-metoxilo, halo-tioalquilo de 1 a 7 átomos de carbono, tal como trifluoro-tiometilo, nitro, carboxilo, alquilo de 1 a 7 átomos de carbono-carbonilo, halo-alquilo de 1 a 7 átomos de carbono-carbonilo, hidroxi-alquilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-carbonilo, halo-alcoxilo de 1 a 7 átomos de carbono-carbonilo, carbamoílo, ciano, alquilo de 1 a 7 átomos de carbono-sulfinilo, sulfonilo, alquilo de 1 a 7 átomos de carbono-sulfonilo, halo-alquilo de 1 a 7 átomos de carbono-sulfonilo, hidroxi-alquilo de 1 a 7 átomos de carbono-sulfonilo, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-sulfonilo, sulfamoílo, y N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino-sulfonilo; o es acilo como justamente se definió bajo R_a, o se selecciona a partir de (fenilo o fenil-alquilo de 1 a 7 átomos de carbono)-sulfonilo insustituido o mono-, di-, o tri-sustituido por (halógeno y/o alquilo de 1 a 7 átomos de carbono), tal como fenil-sulfonilo o fenil-metan-sulfonilo, o alquilo de 1 a 7

átomos de carbono-sulfonilo, tal como metan-sulfonilo;

R_c es hidrógeno, alquilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, o alquiloxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, de preferencia hidrógeno o alquilo de 1 a 7 átomos de carbono;

R_d es fenil- o naftil-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, en donde, en el caso de una fracción sustituida, los sustituyentes son uno o más, en especial hasta tres sustituyentes independientemente seleccionados a partir de aquéllos mencionados para fenil- o naftil-alquilo de 1 a 7 átomos de carbono insustituido o sustituido bajo R_b, o es $-N(R_b)(R_c)$;

R_e es alquilo de 1 a 7 átomos de carbono, o de preferencia hidrógeno; y

m es 2;

cada uno de R^4 y R^5 se selecciona, independiente-mente uno del otro, a partir de alquilo de 1 a 7 átomos de carbono, hidroxi, alquiloxilo de 1 a 7 átomos de carbono, o de preferencia hidrógeno;

y T es carbonilo, o de preferencia metileno;

o una sal farmacéuticamente aceptable del mismo, para el tratamiento de una enfermedad que dependa de la actividad de la renina, en especial hipertensión, o de preferencia para la fabricación de una formulación farmacéutica para el tratamiento de una enfermedad que dependa de la actividad de la renina, en

especial hipertensión.

Una modalidad muy preferida de la invención se refiere a un nuevo compuesto de la Fórmula I, en donde:

R^1, R^3, R^4, R^5, m, y T son como se definen en el párrafo anterior, y

R^2 es fenilo, naftilo, o (con menor preferencia) naftil-alquilo de 1 a 7 átomos de carbono, en donde cada fenilo o naftilo mencionados hasta ahora en la definición de R^2 está insustituido o sustituido como justamente se describió para fenilo o naftilo sustituido en la definición de R^1, o es de preferencia alquilo de 1 a 7 átomos de carbono que está insustituido o sustituido por uno o más, en especial hasta tres, por ejemplo uno o dos sustituyentes independientemente seleccionados a partir del grupo que consiste en alquenilo de 2 a 7 átomos de carbono, alquinilo de 2 a 7 átomos de carbono, halógeno, hidroxi, alcoxilo de 1 a 7 átomos de carbono, halo-alcoxilo de 1 a 7 átomos de carbono, tal como trifluoro-metoxilo, hidroxi-alcoxilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono, fenil- o naftil-oxilo, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono, alcanoiloxilo de 1 a 7 átomos de carbono, benzoil- o naftoil-oxilo, tioalquilo de 1 a 7 átomos de carbono, halo-tioalquilo de 1 a 7 átomos de carbono, tal como trifluoro-tiometilo, hidroxi-tioalquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-tioalquilo de 1 a 7 átomos de carbono, tiofenilo o tionaftilo, fenil- o naftil-tioalquilo de 1 a 7 átomos de

carbono, tioalcanoílo de 1 a 7 átomos de carbono, tiobenzoílo o tionaftoílo, nitro, amino, mono- o di-(alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, y/o alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono)-amino, mono- o di-(naftil- o fenil-alquilo de 1 a 7 átomos de carbono)-amino, alcanoílo de 1 a 7 átomos de carbono-amino, benzoil- o naftoil-amino, alquilo de 1 a 7 átomos de carbono-sulfonil-amino, fenil- o naftil-sulfonil-amino, en donde el fenilo o naftilo está insustituido o sustituido por una o más, en especial por una a tres fracciones de alquilo de 1 a 7 átomos de carbono, fenil- o naftil-alquilo de 1 a 7 átomos de carbono-sulfonil-amino, carboxilo, alquilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, fenil- o naftil-oxicarbonilo, fenil- o naftil-alcoxilo de 1 a 7 átomos de carbono-carbonilo, carbamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, N-mono- o N,N-di-(naftil- o fenil-alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, ciano, sulfenilo (-S-OH), sulfonilo (-S(=O)-OH), alquilo de 1 a 7 átomos de carbono-sulfinilo (alquilo de 1 a 7 átomos de carbono-S(=O)-), fenil- o naftil-sulfinilo, en donde fenilo o naftilo está insustituido o sustituido por una o más, en especial por una a tres fracciones de alquilo de 1 a 7 átomos de carbono, fenil- o naftil-alquilo de 1 a 7 átomos de carbono-sulfinilo, sulfonilo, alquilo de 1 a 7 átomos de carbono-sulfonilo, fenil- o naftil-sulfonilo, en donde el fenilo o naftilo está insustituido o sustituido por una o más, en especial por

una a tres fracciones de alquilo de 1 a 7 átomos de carbono, fenil- o naftil-alquilo de 1 a 7 átomos de carbono-sulfonilo, sulfamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, fenilo, naftilo, fenil-alquilo de 1 a 7 átomos de carbono, o naftil-alquilo de 1 a 7 átomos de carbono)-amino-sulfonilo, N-mono-, N'-mono-, N,N-di-, ó N,N,N'-tri-(alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, y/o alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono)-amino-carbonil-amino, y N-mono-, N'-mono-, N,N-di-, ó N,N,N'-tri-(alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, y/o alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono)-amino-sulfonil-amino; o es cicloalquilo de 3 a 10 átomos de carbono, o ciclo-alquilo de 3 a 10 átomos de carbono-alquilo de 1 a 7 átomos de carbono;

o una sal (de preferencia farmacéuticamente aceptable) del mismo.

En otra modalidad muy preferida, la invención se refiere a un nuevo compuesto de la Fórmula I, en donde:

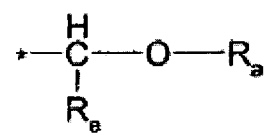
R^1 es fenil-, indolil-, o quinolil-alcanoílo de 1 a 7 átomos de carbono (de preferencia -carbonilo o -acetilo), en donde el fenilo, indolilo, o quinolilo está sustituido por alquiloxilo de 1 a 7 átomos de carbono-alquiloxilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, o alquiloxilo de 1 a 7 átomos de carbono-alquiloxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, y además puede

estar sustituido por una o más, por ejemplo hasta tres fracciones de alquilo de 1 a 7 átomos de carbono (en especial, metilo), y/o alquiloxilo de 1 a 7 átomos de carbono;

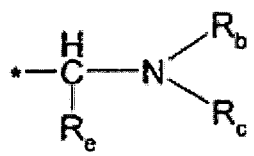
R^2 es alquilo de 1 a 7 átomos de carbono;

R^3 es una fracción seleccionada a partir del grupo de facciones de las fórmulas:

(a)

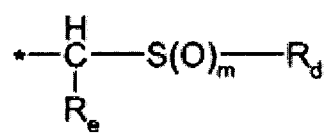


(b)

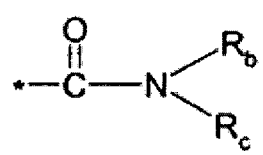


y

(c)



(f)



en donde, en cualquiera de las fracciones de las fórmulas dadas anteriormente bajo (a), (b), (c), y (f), el asterisco (*) muestra el enlace que enlaza a la fracción R^3 respectiva con el

resto de la molécula en la Fórmula I,

en donde:

R_a es hidrógeno, o N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, fenilo o naftilo (insustituido o sustituido por halógeno), fenil-alquilo de 1 a 7 átomos de carbono, naftil-alquilo de 1 a 7 átomos de carbono, o cicloalquilo de 3 a 8 átomos de carbono)-amino-carbonilo;

cada uno de R_b y R_c, independientemente uno del otro, se selecciona a partir de hidrógeno, alquilo de 1 a 7 átomos de carbono, fenilo, naftilo, naftil-alquilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono-carbonilo (= cicloalquilo de 3 a 8 átomos de carbono-C(=O)-), cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono-carbonilo, fenil- o naftil-alcanoílo de 1 a 7 átomos de carbono insustituido o mono-, di-, o tri-sustituido por (halógeno, alcoxilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono-alquiloxilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, y/o alquilo de 1 a 7 átomos de carbono), de preferencia benzoílo o fenil-acetilo, (tetrahidrofuranil o tetrahidropiranil)-carbonilo, o (tetrahidrofuranil o tetrahidropiranil)-alquilo de 1 a 7 átomos de carbono-carbonilo, tal como tetrahidro-furanil-carbonilo, tetrahidro-piranil-carbonilo, tetrahidro-furanil-acetilo, o tetrahidro-piranil-acetilo, alquilo de 1 a 7 átomos de carbono-sulfonilo (= alcano de 1 a 7 átomos de carbono-sulfonilo), o (fenil- o naftil)-alquilo de 1 a 7 átomos de

carbono-sulfonilo (insustituido o sustituido por [alquilo de 1 a 7 átomos de carbono, halo-alquilo inferior, halógeno, alquiloxilo de 1 a 7 átomos de carbono, ciano, alcanoílo de 1 a 7 átomos de carbono, y/o alquilo de 1 a 7 átomos de carbono-sulfonilo]), con la condición de que, si R_c es hidrógeno, alquilo de 1 a 7 átomos de carbono, fenilo, naftilo, o naftil-alquilo de 1 a 7 átomos de carbono, entonces R_b también puede ser fenil-alquilo de 1 a 7 átomos de carbono; R_d es (fenil- o naftil)-alquilo de 1 a 7 átomos de carbono insustituido o sustituido por [alquilo de 1 a 7 átomos de carbono, fenilo, halo-alquilo inferior, halógeno, oxo-alquilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono, fenil-alcoxilo de 1 a 7 átomos de carbono, halo-alquiloxilo de 1 a 7 átomos de carbono, fenoxilo, alcanoílo de 1 a 7 átomos de carbono-amino, ciano, alcanoílo de 1 a 7 átomos de carbono, y/o alquilo de 1 a 7 átomos de carbono-sulfonilo];

R_e es hidrógeno; y

m es 2;

cada uno de R^4 y R^5 es hidrógeno; y

T es carbonilo, o de preferencia metileno;

o una sal (de preferencia farmacéuticamente aceptable) del mismo.

En lo siguiente, se proporcionan las definiciones preferidas individualmente para cada variante. Se debe observar que cada una de las definiciones preferidas para cualquier variante se puede combinar con cualquier definición preferida de otras variantes.

Definiciones preferidas para R^1.

R^1 es como se define en las reivindicaciones, de preferencia R^1 es acilo como se define en la presente, más preferiblemente llevando un grupo carbonilo.

En un primera modalidad, R^1 es aril-carbonilo insustituido o sustituido.

Los ejemplos preferidos para la fracción de arilo del sustituyente de acilo son fenilo y naftilo, más preferible-mente fenilo. Cuando la fracción de arilo está sustituida, de preferencia está mono-, di-, o tri-sustituida, y de una manera más preferible di-sustituida. Los sustituyentes adecuados para la fracción de arilo son como se definen en la presente, de preferencia -(alquileno de 0 a 7 átomos de carbono)-$(X)_r$-(alquileno de 1 a 7 átomos de carbono)-$(Y)_s$-(alquileno de 0 a 7 átomos de carbono)-H, en donde **r** y **s** son 0 ó 1, e Y y X son independientemente O, NH, ó NH-CO-O-; o es halógeno, tal como Cl o F, hidroxi, fenil- o naftil-oxilo, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono, heterociclilo mono-cíclico-alquiloxilo de 1 a 7 átomos de carbono, en donde el heterociclilo es de preferencia un anillo de 5 ó 6 miembros que contiene un átomo de nitrógeno, tal como isoxazolilo; nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, carboxilo, y ciano, más preferiblemente -(alquileno de 0 a 7 átomos de carbono)-$(X)_r$-(alquileno de 1 a 7 átomos de carbono)-$(Y)_s$-(alquileno de 0 a 7 átomos de carbono)-H, heterociclilo monocíclico-alquiloxilo de 1 a 7 átomos de carbono, fenil- o naftil-alquiloxilo de 1 a 7 átomos de

carbono, o halógeno. Cuando las fracciones de alquileno de la Fórmula -(alquileno de 0 a 7 átomos de carbono)-$(X)_r$-(alquileno de 1 a 7 átomos de carbono)-$(Y)_s$-(alquileno de 0 a 7 átomos de carbono)-H están sustituidas, de preferencia están sustituidas por uno o más, y de una manera más preferible tres halógeno, tal como F. Los ejemplos preferidos de -(alquileno de 0 a 7 átomos de carbono)-$(X)_r$-(alquileno de 1 a 7 átomos de carbono)-$(Y)_s$-(alquileno de 0 a 7 átomos de carbono)-H incluyen -(O ó NH, de preferencia O)-alquilo de 1 a 7 átomos de carbono, alquilo de 1 a 7 átomos de carbono, -(O ó NH, de preferencia O)-alquileno de 1 a 7 átomos de carbono-(O ó NH, de preferencia O)-alquilo de 1 a 7 átomos de carbono, -(O ó NH, de preferencia O)-alquileno de 1 a 7 átomos de carbono-(O ó NH, de preferencia O)-H, -alquileno de 1 a 7 átomos de carbono-(O ó NH, de preferencia O)-alquileno de 1 a 7 átomos de carbono-(O ó NH, de preferencia O)-alquilo de 1 a 7 átomos de carbono, -alquileno de 1 a 7 átomos de carbono-(O ó NH, de preferencia O)-alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, -(O ó NH, de preferencia O)-halo-alquilo de 1 a 7 átomos de carbono, ó -(O ó NH, de preferencia O)-alquileno de 1 a 7 átomos de carbono-(O ó NH, de preferencia O)-halo-alquilo de 1 a 7 átomos de carbono, más preferiblemente -OMe, $-OC_3H_6OMe$, metilo, etilo, terbutilo, $-CH_2OC_2H_4OMe$, $-OC_2H_4OC_2H_4$, $-OC_3H_6OH$, $-C_4H_8OMe$, $-CHF_2$, $-OCF_3$, $-OC_2H_4CF_3$, $-OC_3H_6CF_3$, y $-OC_3H_6OCF_3$. En las modalidades preferidas, la fracción de arilo está di-sustituida, en donde ambos

sustituyentes son -(alquileno de 0 a 7 átomos de carbono)-$(X)_r$-(alquileno de 1 a 7 átomos de carbono)-$(Y)_s$-(alquileno de 0 a 7 átomos de carbono)-H como se define en la presente, más preferiblemente un sustituyente es -O-alquilo de 1 a 7 átomos de carbono, tal como OMe, o -alquilo de 1 a 7 átomos de carbono, tal como metilo o etilo, y el otro el -O-alquileno de 1 a 7 átomos de carbono-O-alquilo de 1 a 7 átomos de carbono, tal como -OC_3H_6OMe.

En una segunda modalidad, R^1 es heterociclil-carbonilo insustituido o sustituido.

Los ejemplos preferidos para la fracción de hetero-ciclilo del sustituyente de acilo son heterociclilo mono- o bi-cíclico, de preferencia bicíclico. Se prefieren los sistemas de anillo aromático, o en particular si se contempla una fracción bicíclica, los sistemas de anillo parcialmente saturados, en particular en donde uno de los anillos es aromático y el otro está saturado. Se prefieren más los sistemas de anillo aromáticos. La fracción de heterociclilo de preferencia tiene 1, 2, ó 3, más preferiblemente 1 ó 2 heteroátomos seleccionados a partir de O, N, o S, más preferiblemente O o N. Los ejemplos particularmente preferidos incluyen pirrolilo, furanilo, tienilo (= tiofenilo), tiazolilo, pirazolilo, triazolilo, tetrazolilo, oxetidinilo, 3-(alquilo de 1 a 7 átomos de carbono)-oxetidinilo, piridilo, pirimidinilo, morfolino, tio-morfolino, piperidinilo, piperazinilo, pirrolidinilo, tetrahidro-furanilo, tetrahidrofuran-onilo, tetrahidro-piranilo, 1H-indazolilo,

benzofuranilo, benzotiofenilo, bencimidazolilo, benzopirazolilo, benzo[1,2,5]oxadiazolilo, y 3,4-dihidro-2H-benzo[1,4]dioxinilo, o de una manera más preferible indolilo, isoquinolilo, quinolilo, y 3,4-dihidro-2H-benzo[1,4]dioxinilo, o en especial indolilo, y 3,4-dihidro-2H-benzo[1,4]dioxinilo. Cuando la fracción de heterociclilo está sustituida, de preferencia está mono-, di-, o tri-sustituida, y de una manera más preferible di-sustituida. Los sustituyentes adecuados para la fracción de heterociclilo son como se definen en la presente, de preferencia -(alquileno de 0 a 7 átomos de carbono)-$(X)_r$-(alquileno de 1 a 7 átomos de carbono)-$(Y)_s$-(alquileno de 0 a 7 átomos de carbono)-H, en donde r y s son 0 ó 1, e Y y X son independientemente O, NH, ó NH-CO-O-; halo-alquilo de 1 a 7 átomos de carbono, halógeno, hidroxi, fenil- o naftil-oxilo, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, carboxilo, y ciano. Los ejemplos preferidos de -(alquileno de 0 a 7 átomos de carbono)-$(X)_r$-(alquileno de 1 a 7 átomos de carbono)-$(Y)_s$-(alquileno de 0 a 7 átomos de carbono)-H incluyen -(O ó NH, de preferencia O)-alquilo de 1 a 7 átomos de carbono, alquilo de 1 a 7 átomos de carbono, -(O ó NH, de preferencia O)-alquileno de 1 a 7 átomos de carbono-(O ó NH, de preferencia O)-alquilo de 1 a 7 átomos de carbono, -(O ó NH, de preferencia O)-alquileno de 1 a 7 átomos de carbono-(O ó NH, de preferencia O)-H, -alquileno de 1 a 7 átomos de carbono-(O ó NH, de preferencia O)-alquileno de 1 a 7 átomos de carbono-(O ó NH, de preferencia O)-alquilo de 1 a 7

átomos de carbono, -alquileno de 1 a 7 átomos de carbono-(O ó NH, de preferencia O)-alquilo de 1 a 7 átomos de carbono, más preferiblemente -alquilo de 1 a 7 átomos de carbono, -O-alquileno de 1 a 7 átomos de carbono-O-alquilo de 1 a 7 átomos de carbono, o -alquileno de 1 a 7 átomos de carbono-O-alquilo de 1 a 7 átomos de carbono, todavía de una manera más preferible metilo, etilo, C_2H_4-NH-CO-OMe, $-CH_2OC_2H_4OMe$, $-OC_2H_4OC_2H_4$, $-OC_3H_6OH$, $-C_2H_4OMe$, $-C_3H_6OMe$, y -NH-C_3H_6OMe, y todavía de una manera muy preferible -metilo, $-OC_3H_6OCF_3$, y $-C_3H_6OMe$. De una forma muy preferible, la fracción de heterociclilo está sustituida por metilo y/o $-C_3H_6OMe$.

Definiciones preferidas para R^2.

R^2 es como se define en las reivindicaciones; de preferencia R^2 es, en una primera modalidad, alquilo insustituido o sustituido como se define en la presente. Los ejemplos preferidos son alquilo de 1 a 7 átomos de carbono de cadena ramificada o recta, el cual puede estar sustituido o insustituido. En una modalidad preferida, R^2 es alquilo ramificado, tal como isopropilo, isobutilo, butilo secundario o butilo terciario, isopentilo, 1-etil-propilo, y 1,2-dimetil-propilo, y muy preferiblemente isopropilo. Alquilo ramificado de preferencia está insustituido. Si la fracción de alquilo está sustituida, los sustituyentes adecuados son como se definen en la presente, de preferencia O-alquilo de 1 a 4 átomos de carbono, halógeno, hidroxi, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-alquiloxilo de

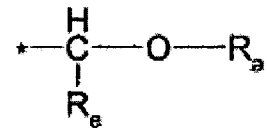
1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, carboxilo, y ciano.

De preferencia, en una segunda modalidad, R^2 es cicloalquilo. Los ejemplos preferidos para la fracción de cicloalquilo son los anillos monocíclicos, de preferencia cicloalquilo de 3 a 7 átomos de carbono, más preferiblemente cicloalquilo de 3, 4, 5, y 6 átomos de carbono, y de una manera muy preferible ciclopropilo. La fracción de ciclo-alquilo puede estar sustituida o insustituida. Cuando la fracción de cicloalquilo está sustituida, de preferencia está mono-sustituida. Los sustituyentes adecuados para la fracción de cicloalquilo son como se definen en la presente, de preferencia O-alquilo de 1 a 4 átomos de carbono, halógeno, hidroxi, fenilo insustituido o sustituido, naftilo, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, carboxilo, y ciano, más preferiblemente fenilo o naftilo. De una forma muy preferible, la fracción de cicloalquilo está insustituida.

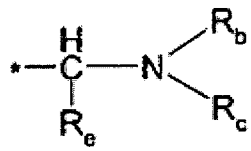
Definiciones preferidas para R^3.

R^3 es como se define en las reivindicaciones; de preferencia R^3 es una fracción seleccionada a partir del grupo que fracciones de las fórmulas:

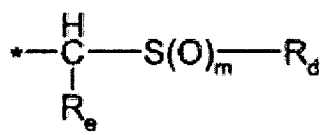
(a)



(b)

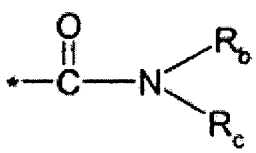


(c)



y

(f)



más preferiblemente (a), (b), ó (f), todavía de una manera más preferible (a) ó (b), de una forma más preferible (b), en donde, en cualquiera de las fracciones de las fórmulas dadas anteriormente bajo (a), (b), (c), y (f), el asterisco (*) muestra el enlace que enlaza a la fracción R^3 respectiva con el resto de la molécula en la Fórmula I,

en donde:

R_a es acilo seleccionado a partir de alcanoílo de 1 a 7 átomos de carbono, fenil-alcanoílo de 1 a 7 átomos de carbono

insustituido o mono-, di-, o tri-sustituido por (halo-alcoxilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono-alquiloxilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, y/o alquilo de 1 a 7 átomos de carbono), cicloalquilo de 3 a 8 átomos de carbono-carbonilo, o cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono-carbonilo, (tetrahidro-furanil o tetrahidro-piranil)-carbonilo, o (tetrahidrofuranil o tetrahidropiranil)-alquilo de 1 a 7 átomos de carbono-carbonilo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, N-[fenil, o fenil-alquilo de 1 a 7 átomos de carbono]-amino-carbonilo, N-[cicloalquilo de 3 a 8 átomos de carbono o cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono]-amino-carbonilo, alquilo de 1 a 7 átomos de carbono-amino-carbonilo, N-(fenil-alquilo de 1 a 7 átomos de carbono)(alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, N-(fenil-alquilo de 1 a 7 átomos de carbono)-(cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, N-(alquilo de 1 a 7 átomos de carbono)(cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, N-(fenil-alquilo de 1 a 7 átomos de carbono)(cicloalquilo de 3 a 8 átomos de carbono)-amino-carbonilo, N-(heterociclil-alquilo de 1 a 7 átomos de carbono)(cicloalquilo de 3 a 8 átomos de carbono)-amino-carbonilo, N-(heterociclil)(cicloalquilo de 3 a 8 átomos de carbono)-amino-carbonilo; o es hidrógeno;

R_b es alquilo de 1 a 7 átomos de carbono o fenilo, naftilo, fenil-alquilo de 1 a 7 átomos de carbono, o naftil-alquilo de 1 a 7 átomos de carbono - en cada caso insustituido o sustituido -, en donde, en el caso de una fracción sustituida, los sustituyentes son uno o más, en especial hasta tres sustituyentes independientemente seleccionados a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono, alquenilo de 2 a 7 átomos de carbono, alquinilo de 2 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, tal como trifluoro-metilo, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, amino-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono, hidroxi-alcoxilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono, alcanoiloxilo de 1 a 7 átomos de carbono, amino, mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino, alcanoílo de 1 a 7 átomos de carbono-amino, alquilo de 1 a 7 átomos de carbono-sulfonil-amino, alcoxilo de 1 a 7 átomos de carbono-carbonilo, carboxi-alquilo de 1 a 7 átomos de carbono, halógeno, hidroxi, halo-alcoxilo de 1 a 7 átomos de carbono, halo-tioalquilo de 1 a 7 átomos de carbono, nitro, carboxilo, alquilo de 1 a 7 átomos de carbono-carbonilo, halo-alquilo de 1 a 7 átomos de carbono-carbonilo, hidroxi-alquilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-carbonilo, halo-alcoxilo de 1 a 7 átomos de carbono-carbonilo, carbamoílo, ciano,

alquilo de 1 a 7 átomos de carbono-sulfinilo, sulfonilo, alquilo de 1 a 7 átomos de carbono-sulfonilo, halo-alquilo de 1 a 7 átomos de carbono-sulfonilo, hidroxi-alquilo de 1 a 7 átomos de carbono-sulfonilo, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-sulfonilo, sulfamoílo, y N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino-sulfonilo; o es acilo como justamente se definió bajo R_a, o se selecciona a partir de (fenilo o fenil-alquilo de 1 a 7 átomos de carbono)-sulfonilo insustituido o mono-, di-, o tri-sustituido por (halógeno y/o alquilo de 1 a 7 átomos de carbono), alquilo de 1 a 7 átomos de carbono-sulfonilo;

R_c es hidroxi-alquilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono, o de preferencia hidrógeno, cicloalquilo de 3 a 8 átomos de carbono insustituido o sustituido, o alquilo de 1 a 7 átomos de carbono insustituido o sustituido;

R_d es fenil- o naftil-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, en donde, en el caso de una fracción sustituida, los sustituyentes son uno o más, en especial hasta tres sustituyentes independientemente seleccionados a partir de aquéllos mencionados para fenil- o naftil-alquilo de 1 a 7 átomos de carbono insustituido o sustituido bajo R_b, o es $-N(R_b)(R_c)$;

R_e es alquilo de 1 a 7 átomos de carbono, o de preferencia hidrógeno; y

m es 2;

de preferencia, R_a es hidrógeno, o N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, fenilo o naftilo (insustituido o sustituido por halógeno), fenil-alquilo de 1 a 7 átomos de carbono, naftil-alquilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono, heterociclil-alquilo de 1 a 7 átomos de carbono, heterociclilo, y/o cicloalquilo de 3 a 8 átomos de carbono)-amino-carbonilo;

cada uno de R_b y R_c, independientemente uno del otro, se selecciona a partir de hidrógeno, alquilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, arilo insustituido o sustituido tal como fenilo, naftilo, naftil-alquilo de 1 a 7 átomos de carbono, o acilo, tal como cicloalquilo de 3 a 8 átomos de carbono-carbonilo, cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono-carbonilo, fenil- o naftil-alcanoílo de 1 a 7 átomos de carbono-carbonilo, fenil- o naftil-alcanoílo de 1 a 7 átomos de carbono insustituido o mono-, di-, o tri-sustituido por (halógeno, alcoxilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono-alquiloxilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, y/o alquilo de 1 a 7 átomos de carbono), (tetrahidrofuranil o tetrahidropiranil)-carbonilo, o (tetrahidrofuranil o tetrahidropiranil)-alquilo de 1 a 7 átomos de carbono-carbonilo, alquilo de 1 a 7 átomos de carbono-sulfonilo, o

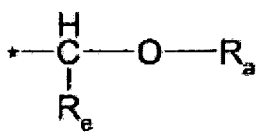
(fenil- o naftil)-alquilo de 1 a 7 átomos de carbono-sulfonilo (insustituido o sustituido por [alquilo de 1 a 7 átomos de carbono, halo-alquilo inferior, halógeno, alquiloxilo de 1 a 7 átomos de carbono, ciano, alcanoílo de 1 a 7 átomos de carbono, y/o alquilo de 1 a 7 átomos de carbono-sulfonilo]), con la condición de que, si R_c es hidrógeno, alquilo de 1 a 7 átomos de carbono, fenilo, naftilo, o naftil-alquilo de 1 a 7 átomos de carbono, entonces R_b también puede ser fenil-alquilo de 1 a 7 átomos de carbono;

R_d es (fenil- o naftil)-alquilo de 1 a 7 átomos de carbono insustituido o sustituido por [alquilo de 1 a 7 átomos de carbono, fenilo, halo-alquilo inferior, halógeno, oxo-alquilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono, fenil-alcoxilo de 1 a 7 átomos de carbono, halo-alquiloxilo de 1 a 7 átomos de carbono, fenoxilo, alcanoílo de 1 a 7 átomos de carbono-amino, ciano, alcanoílo de 1 a 7 átomos de carbono, y/o alquilo de 1 a 7 átomos de carbono-sulfonilo];

R_e es hidrógeno; y

m es 2.

R^3 es, en una primera modalidad, una fracción de la Fórmula (a):



En esta modalidad, R_a es como se define en la presente, de preferencia R_a es hidrógeno o acilo, de preferencia acilo. Acilo de

preferencia se selecciona a partir de alcanoílo de 1 a 7 átomos de carbono, fenil-alcanoílo de 1 a 7 átomos de carbono insustituido o mono-, di-, o tri-sustituido por (halógeno, alcoxilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono-alquiloxilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, y/o alquilo de 1 a 7 átomos de carbono), cicloalquilo de 3 a 8 átomos de carbono-carbonilo, o cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono-carbonilo, (tetrahidro-furanil o tetrahidro-piranil)-carbonilo, o (tetrahidrofuranil o tetrahidropiranil)-alquilo de 1 a 7 átomos de carbono-carbonilo, y (alquilo de 1 a 7 átomos de carbono, fenilo, naftilo, fenil-alquilo de 1 a 7 átomos de carbono, y/o naftil-alquilo de 1 a 7 átomos de carbono)-oxicarbonilo, o de preferencia a partir de amino-carbonilo N-mono- o N,N-di-sustituido, en particular N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, tal como N,N-di-(CH_2CHCH_3)-amino-carbonilo, o N-(CH_2CHCH_3)(metil)-amino-carbonilo, N-[fenil, o fenil-alquilo de 1 a 7 átomos de carbono, tal como fenil-CH_2-, o como fenil-$CH(CH_2CH_3)$-]-amino-carbonilo, N-[cicloalquilo de 3 a 8 átomos de carbono o cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono]-amino-carbonilo, alquilo de 1 a 7 átomos de carbono-amino-carbonilo, N-(fenil-alquilo de 1 a 7 átomos de carbono)(alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, tal como N-(fenil-CH_2-)(metil o etil)-amino-carbonilo, N-(fenil-alquilo de 1 a 7 átomos de carbono)-(cicloalquilo de 3 a 8

átomos de carbono-alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, tal como N-(fenil-CH_2-) (ciclopropil-CH_2-)-amino-carbonilo, N-(alquilo de 1 a 7 átomos de carbono)(cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, tal como N-(metil)(ciclohexil-CH_2-)-amino-carbonilo, N-(fenil-alquilo de 1 a 7 átomos de carbono)(cicloalquilo de 3 a 8 átomos de carbono)-amino-carbonilo, tal como N-(fenil-CH_2-) (ciclopropil)-amino-carbonilo, N-(heterociclil-alquilo de 1 a 7 átomos de carbono)(cicloalquilo de 3 a 8 átomos de carbono)-amino-carbonilo, tal como N-(heterociclil-alquilo de 1 a 7 átomos de carbono)(ciclopropil)-amino-carbonilo, y N-(heterociclil)(cicloalquilo de 3 a 8 átomos de carbono)-amino-carbonilo, tal como N-(heterociclil)(ciclopropil)-amino-carbonilo, en donde el heterociclilo en cada caso es de preferencia un sistema de anillo o sistema de anillo aromático monocíclico, tal como monocíclico de 5 ó 6 miembros, de preferencia saturado, en particular un sistema de anillo saturado. La fracción de heterociclilo tiene de preferencia 1, 2, ó 3, más preferiblemente 1 ó 2 hetero-átomos seleccionados a partir de O, N, ó S, y de una manera muy preferible O ó N. Los ejemplos particularmente preferidos incluyen anillos de 5 ó 6 miembros que contengan de preferencia un átomo de oxígeno, en particular tetrahidro-piranilo o tetrahidro-furanilo. Cuando la fracción de hetero-ciclilo está sustituida, de preferencia está mono-sustituida. Los sustituyentes adecuados para la fracción de heterociclilo son como se definen en

la presente, de preferencia halógeno, hidroxi, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, carboxilo, y ciano, más preferiblemente fenil-alquilo de 1 a 7 átomos de carbono. Los sustituyentes de fenilo adecuados incluyen alquilo de 1 a 7 átomos de carbono, -O-alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, halógeno, hidroxi, y amino. De una manera muy preferible, la fracción de heterociclilo está insustituida.

En esta modalidad, R_e es como se define en la presente, de preferencia R_e es hidrógeno.

Cuando R^3 es una fracción de la Fórmula (a), entonces uno o más, de preferencia todos los siguientes sustituyentes, tienen la siguiente definición:

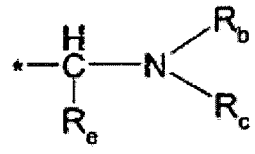
R^1 es fenil-carbonilo sustituido como se define en la presente, en particular en donde un sustituyente es -O-alquilo de 1 a 7 átomos de carbono, tal como OMe, o -alquilo de 1 a 7 átomos de carbono, tal como metilo o etilo, y el otro es -O-alquileno de 1 a 7 átomos de carbono-O-alquilo de 1 a 7 átomos de carbono, tal como $-OC_3H_6OMe$; o R^1 es hetero-ciclil-carbonilo aromático sustituido, en particular hetero-ciclil-carbonilo bicíclico, tal como indolil-carbonilo, en donde la fracción de heterociclilo está sustituida por metilo y/o $-C_3H_6OMe$;

R^2 es alquilo ramificado, tal como isopropilo;

T es metileno, y

R^4 y R^5 son hidrógeno.

R^3 es, en una segunda modalidad, una fracción de la Fórmula (b):



En esta modalidad, R_b es como se define en la presente, de preferencia R_b se selecciona a partir de hidrógeno, alquilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, arilo insustituido o sustituido, tal como fenilo, naftilo, naftil-alquilo de 1 a 7 átomos de carbono, o acilo, más preferiblemente arilo o acilo insustituido o sustituido, y de una manera muy preferible acilo, cada uno como se define en la presente.

Cuando R_b es arilo insustituido o sustituido, los ejemplos preferidos son fenilo o naftilo, más preferiblemente fenilo, los cuales están cada uno insustituido o sustituido por un sustituyente adecuado, tal como alquilo de 1 a 7 átomos de carbono, -O-alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, halógeno, hidroxi, fenil- o naftil-oxilo, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, carboxilo, y ciano; de preferencia, cada uno está insustituido.

Cuando R_b es acilo, los ejemplos preferidos se seleccionan a partir del grupo que consiste en (a) a (p), más preferiblemente (e):

(a) Arilo mono- o bi-cíclico-carbonilo insustituido o sustituido.

Los ejemplos preferidos de la fracción de arilo incluyen arilo mono- o bi-cíclico con 6 a 22 átomos de carbono, en donde uno de los anillos del arilo bicíclico puede ser un anillo parcial o completamente saturado condensado con el otro anillo aromático, en especial fenilo, indanilo, indenilo, 1,2,3,4-tetrahidro-naftilo, o naftilo, más preferiblemente fenilo, indanilo, ó 1,2,3,4-tetrahidro-naftilo. Cuando la fracción de arilo está sustituida, de preferencia está mono- o di-sustituida. En particular, fenilo de preferencia está insustituido, mono- o di-sustituido, e indanilo o 1,2,3,4-tetrahidro-naftilo de preferencia están insustituidos. Los sustituyentes adecuados son como se definen en la presente, de preferencia alquilo de 1 a 7 átomos de carbono, -O-alquilo de 1 a 7 átomos de carbono, tal como OMe, halo-alquilo de 1 a 7 átomos de carbono, halógeno, tal como Cl, -O-alquileno de 1 a 7 átomos de carbono-O-alquilo, tal como $O\text{-}C_3H_6OCH_3$, hidroxi, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, carboxilo, y ciano, heterociclilo insustituido o sustituido, de preferencia insustituido, o heterociclil-alquilo de 1 a 4 átomos de carbono insustituido o sustituido, de preferencia insustituido, tal como heterociclilo-CH_2, en donde la fracción de heterociclilo en cada caso es de preferencia heterociclilo monocíclico de 5 ó 6 miembros, que contiene preferiblemente un

átomo de N y/u O, tal como tetrahidro-furanilo o tetra-hidro-piranilo, piperidinilo, pirrolidinilo, piperazinilo, o morfolinilo, de una manera más preferible heterociclilo, heterociclilo-CH_2-, -O-alquilo de 1 a 7 átomos de carbono, -O-alquileno de 1 a 7 átomos de carbono-O-alquilo, y/o halógeno.

(b) Heterociclilo mono- o bi-cíclico-carbonilo insustituido o sustituido.

Los ejemplos preferidos para la fracción de hetero-ciclilo son anillos mono- o bi-cíclicos. Se prefieren los sistemas de anillo de 3 a 14, más preferiblemente de 5 a 11. La fracción de heterociclilo puede ser saturada, parcialmente saturada, o aromática, en particular si se contempla una fracción monocíclica, anillos aromáticos o saturados, o, en particular si se contempla una fracción bicíclica, sistemas de anillo aromáticos o parcialmente saturados, en particular en donde uno de los anillos es aromático y el otro está saturado o parcialmente saturado. La fracción de heterociclilo tiene de preferencia 1, 2, ó 3, más preferiblemente 1 ó 2 hetero-átomos seleccionados a partir de O, N, ó S, más preferible-mente O ó N. Los ejemplos particularmente preferidos incluyen los anillos de 5 ó 6 miembros que contengan de preferencia un átomo de nitrógeno o de oxígeno, en particular pirrolidinilo, oxazolilo, pirrolidin-2-onilo, pirrolilo, piperidilo, furanilo, pirimidilo, piridilo, pirazinilo, isoxazolilo, pirrolidin-2-onilo, tetrahidro-furanilo, o tetrahidro-piranilo; o sistemas de anillo bicíclicos de 9 a 11 miembros que contengan de preferencia

cuando menos un átomo de nitrógeno y/o de oxígeno, en particular indolilo, 2,3-dihidro-benzo-[1,4]-dioxinilo, cromanilo, 2H-cromenilo, 3,4-dihidro-1H-quinolin-2-onilo, benzo-[d]-isoxazolilo, 4,5,6,7-tetrahidro-benzo-[d]-isoxazolilo, 3a,4,5,6,7,7a-hexahidro-benzo-[d]-isoxazolilo, 1,4,5,6-tetrahidro-ciclopentapirazolilo, 3,4-dihidro-2H-benzo-[b]-[1,4]-dioxepinilo, benzofuranilo, 4H-benzo-[1,4]-oxazin-3-onilo, benzo-oxazolilo, benzo-[1,2,5]-oxadiazolilo, bencimidazolilo, ó 3,4-dihidro-2H-benzo-[1,4]-oxazinilo, más preferiblemente pirazinilo, isoxazolilo, pirrolidin-2-onilo, tetrahidro-furanilo, tetrahidro-piranilo, indolilo, 2,3-dihidro-benzo-[1,4]-dioxinilo, cromanilo, 2H-cromenilo, 3,4-dihidro-1H-quinolin-2-onilo, benzo-[d]-isoxazolilo, 4,5,6,7-tetrahidro-benzo-[d]-isoxazolilo, 3a,4,5,6,7,7a-hexahidro-benzo-[d]-isoxazolilo, 1,4,5,6-tetrahidro-ciclopentapirazolilo, ó 3,4-dihidro-2H-benzo-[b]-[1,4]-dioxepinilo. Cuando la fracción de heterociclilo está sustituida, de preferencia está mono-sustituida. Los sustituyentes adecuados para la fracción de heterociclilo son como se definen en la presente, de preferencia -alquilo de 1 a 7 átomos de carbono, tal como metilo, halógeno, hidroxi, alcanoílo de 1 a 7 átomos de carbono, fenilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, cicloalquilo de 3 a 8 átomos de carbono insustituido o sustituido, de preferencia insustituido, tal como ciclopropilo, nitro, amino,

amino-alquilo de 1 a 7 átomos de carbono, carboxilo, y ciano, más preferiblemente fenilo, -alquilo de 1 a 7 átomos de carbono, o cicloalquilo de 3 a 8 átomos de carbono. Los sustituyentes adecuados de fenilo y cicloalquilo incluyen alquilo de 1 a 7 átomos de carbono, -O-alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, halógeno, hidroxi, y amino. De una manera más preferible, la fracción de heterociclilo está insustituida o está mono-sustituida con fenilo, -alquilo de 1 a 7 átomos de carbono, o cicloalquilo de 3 a 8 átomos de carbono.

(c) Cicloalquilo mono- o bi-cíclico-carbonilo insustituido o sustituido.

Los ejemplos preferidos para la fracción de ciclo-alquilo son anillos monocíclicos, de preferencia cicloalquilo de 3 a 8 átomos de carbono, más preferiblemente ciclo-alquilo de 3, 4, 5, 6, y 7 átomos de carbono. La fracción de cicloalquilo puede estar sustituida o insustituida. Cicloalquilo de 3, 4, 5, y 7 átomos de carbono de preferencia está insustituido, y cicloalquilo de 6 átomos de carbono de preferencia está insustituido o sustituido. Cuando la fracción de cicloalquilo está sustituida, de preferencia está mono-sustituida. Los sustituyentes adecuados para la fracción de cicloalquilo son como se definen en la presente, de preferencia O-alquilo de 1 a 4 átomos de carbono, tal como OMe, halógeno, hidroxi, fenilo insustituido o sustituido, naftilo, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, de

preferencia insustituido, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono-amino, carboxilo, y ciano, más preferiblemente O-alquilo de 1 a 4 átomos de carbono o hidroxi.

(d) Alquil-carbonilo insustituido o sustituido.

Los ejemplos preferidos para la fracción de alquilo son alquilo de 1 a 7 átomos de carbono de cadena ramificada o recta, el cual puede estar sustituido o insustituido. En una modalidad, la fracción de alquilo es alquilo ramificado, tal como isopropilo, isobutilo, butilo secundario o butilo terciario, isopentilo, 1-etil-propilo, 2,2-dimetil-propilo, y 1,2-dimetil-propilo, más preferiblemente isobutilo, isopentilo, y 2,2-dimetil-propilo. En otra modalidad, la fracción de alquilo es alquilo de cadena recta, tal como metilo, etilo, propilo normal, butilo normal o pentilo normal, de una manera preferible metilo, etilo, o propilo normal. Alquilo de preferencia está sustituido. Cuando la fracción de alquilo está sustituida, de preferencia está mono-, di-, o tri-sustituida, más preferiblemente mono-sustituida. Los sustituyentes adecuados para la fracción de alquilo son como se definen en la presente, de preferencia O-alquilo de 1 a 4 átomos de carbono, tal como OMe, halógeno, hidroxi, fenil- o naftil-oxilo insustituido o sustituido, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, nitro, amino-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono-amino, tal como -NHCOMe, amino-carbonilo, amino-carbonilo N-mono- o

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N,N-di-sustituido, tal como CONHMe, carboxilo, alquiloxilo de 1 a 7 átomos de carbono-carbonilo, tal como COOMe, y ciano, en donde los sustituyentes de fenilo o naftilo adecuados incluyen alquilo de 1 a 7 átomos de carbono, tal como metilo, -O-alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, halógeno, hidroxi y amino, de preferencia alquilo de 1 a 7 átomos de carbono, y en donde los sustituyentes de amino adecuados incluyen alquilo de 1 a 7 átomos de carbono, tal como metilo, fenilo o ciclopropilo, de preferencia alquilo de 1 a 7 átomos de carbono. De una manera más preferible, la fracción de alquilo está mono-sustituida por -O-alquilo de 1 a 7 átomos de carbono, hidroxi, alcanoílo de 1 a 7 átomos de carbono-amino, feniloxilo insustituido o di-sustituido, aminocarbonilo, aminocarbonilo N-mono- o N,N-di-sustituido, y alquiloxilo de 1 a 7 átomos de carbono-carbonilo.

(e) Arilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono-carbonilo insustituido o sustituido.

De preferencia, aril-alquilo es aril-alquilo de 1 a 6 átomos de carbono, más preferiblemente aril-alquilo de 1 a 4 átomos de carbono, en particular aril-CH_2-, aril-CH_2CH_2-, aril-$CH(CH_3)$-, aril-$CH_2CH(CH_3)$-, o aril-$C(CH_3)_2$-, de una manera más preferible aril-CH_2-. La fracción de alquilo en particular cuando aril-alquilo es aril-CH_2- o aril-CH_2CH_2-, puede estar sustituida, de preferencia mono-sustituida. Los ejemplos de los sustituyentes preferidos incluyen O-alquilo de 1 a 4 átomos de carbono, tal como OMe,

halógeno, hidroxi, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono-amino, tal como -NHCOMe, carboxilo, y ciano, o fenilo insustituido o sustituido, de preferencia insustituido, en donde los sustituyentes de fenilo adecuados incluyen alquilo de 1 a 7 átomos de carbono, -O-alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, halógeno, hidroxi, y amino; de una manera muy preferible, fenilo insustituido, alcanoílo de 1 a 7 átomos de carbono-amino, O-alquilo de 1 a 4 átomos de carbono, o hidroxi.

Los ejemplos preferidos de la fracción de arilo incluyen arilo mono- o bi-cíclico con 6 a 22 átomos de carbono, en donde uno de los anillos del arilo bicíclico puede ser un anillo parcial o completamente saturado condensado con el otro anillo aromático, en especial fenilo, indanilo, indenilo, 1,2,3,4-tetrahidro-naftilo, o naftilo; más preferiblemente fenilo o naftilo. Cuando la fracción de arilo está sustituida, de preferencia está mono-, di-, ó tri-sustituida. En particular, fenilo está de preferencia insustituido, mono-, di-, o tri-sustituido, y naftilo está de preferencia insustituido. En una modalidad, fenilo está de preferencia insustituido. Los sustituyentes adecuados son como se definen en la presente, de preferencia alquilo de 1 a 7 átomos de carbono, -O-alquilo de 1 a 7 átomos de carbono, tal como OMe, halo-alquilo de 1 a 7 átomos de carbono, tal como CF_3, halógeno, tal como Cl o F, -O-alquileno de 1 a 7 átomos de carbono-O-alquilo, tal como -O-$C_3H_6OCH_3$, hidroxi, fenilo o naftilo insustituido o sustituido, de

preferencia sustituido, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono-amino, tal como -NHCOMe, carboxilo, y ciano. Los sustituyentes adecuados para el sustituyente de fenilo y naftilo sobre la fracción de arilo del aril-alquil-carbonilo incluyen alquilo de 1 a 7 átomos de carbono, -O-alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, halógeno, hidroxi, y amino. De una manera muy preferible, la fracción de aril-alquilo está insustituida o sustituida por -O-alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, fenilo sustituido, alcanoílo de 1 a 7 átomos de carbono-amino, y/o halógeno.

(f) Heterociclil-alquilo de 1 a 7 átomos de carbono-carbonilo insustituido o sustituido.

De preferencia el heterociclil-alquilo es hetero-ciclil-alquilo de 1 a 6 átomos de carbono, más preferible-mente heterociclil-alquilo de 1 a 4 átomos de carbono, en particular heterociclil-CH_2-, heterociclil-CH_2CH_2-, o heterociclil-$CH_2C(CH_3)_2$-, más preferiblemente heterociclil-CH_2-. Se prefiere en particular heterociclil-$CH_2C(CH_3)_2$- cuando la fracción de heterociclilo es un anillo de 5 ó 6 miembros, tal como un anillo aromático, en particular pirrolilo. Se prefiere en particular heterociclil-CH_2CH_2-

cuando la fracción de heterociclilo es un anillo de 5 ó 6 miembros, tal como un anillo aromático, en particular furanilo.

Los ejemplos preferidos para la fracción de heterociclilo son los anillos mono- o bi-cíclicos. Se prefieren los sistemas de anillo de 3 a 14, más preferiblemente de 5 a 11 miembros. La fracción de heterociclilo puede estar saturada, parcialmente saturada, o aromática, en particular si se contempla una fracción monocíclica, anillos aromáticos o saturados, o en particular si se contempla una fracción bicíclica, sistemas de anillo aromáticos o parcialmente saturados, en particular en donde uno de los anillos es aromático y el otro está saturado o parcialmente saturado. La fracción de heterociclilo tiene de preferencia 1, 2, ó 3, más preferiblemente 1 ó 2 heteroátomos seleccionados a partir de O, N, ó S, de una manera más preferible O ó N. Los ejemplos particularmente preferidos incluyen los anillos de 5 ó 6 miembros que contengan de preferencia un átomo de nitrógeno o un átomo de oxígeno, en particular pirrolidinilo, oxazolilo, pirimidilo, piridilo, pirazinilo, isoxazolilo, pirrolidin-2-onilo, pirrolilo, piperidilo, furanilo, tetrahidro-furanilo, o tetrahidro-piranilo; o sistemas de anillo bicíclicos de 9 a 11 miembros que contengan de preferencia cuando menos un átomo de nitrógeno y/u oxígeno, en particular 4H-benzo[1,4]oxazin-3-onilo, benzo-oxazolilo, indolilo, 2,3-dihidro-benzo[1,4]dioxinilo, cromanilo, 2H-cromenilo, 3,4-dihidro-1H-quinolin-2-onilo, benzo[d]isoxazolilo, 4,5,6,7-tetrahidro-benzo[d]isoxazolilo, 3a,4,5,6,7,7a-hexahidro-benzo [d]isoxazolilo,

1,4,5,6-tetrahidro-ciclopenta-pirazolilo, 3,4-dihidro-2H-benzo[b][1,4]dioxepinilo, benzofuranilo, benzo-[1,2,5]oxadiazolilo, bencimidazolilo, ó 3,4-dihidro-2H-benzo-[1,4]oxazinilo, más preferiblemente pirrolidinilo, pirrolidin-2-onilo, pirrolilo, piperidilo, furanilo, tetrahidro-furanilo, tetrahidro-piranilo, 4H-benzo[1,4]oxazin-3-onilo, o benzo-oxazolilo. Cuando la fracción de heterociclilo está sustituida, de preferencia está mono-sustituida. Los sustituyentes adecuados para la fracción de heterociclilo son como se definen en la presente, de preferencia -alquilo de 1 a 7 átomos de carbono, tal como metilo, halógeno, hidroxi, alcanoílo de 1 a 7 átomos de carbono, fenilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, cicloalquilo de 3 a 8 átomos de carbono insustituido o sustituido, de preferencia insustituido, tal como ciclopropilo, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, carboxilo, y ciano, más preferiblemente -alquilo de 1 a 7 átomos de carbono o alcanoílo de 1 a 7 átomos de carbono. Los sustituyentes de fenilo y cicloalquilo adecuados incluyen alquilo de 1 a 7 átomos de carbono, -O-alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, halógeno, hidroxi, y amino. De una manera muy preferible, la fracción de heterociclilo está insustituida o está mono-sustituida con fenilo insustituido, -alquilo de 1 a 7 átomos de carbono, o alcanoílo de 1 a 7 átomos de carbono.

(g) Cicloalquilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono-carbonilo insustituido o sustituido.

De preferencia, cicloalquil-alquilo es cicloalquil-alquilo de 1 a 6 átomos de carbono, más preferiblemente cicloalquil-alquilo de 1 a 4 átomos de carbono, en particular cicloalquil-CH_2-, cicloalquil-CH_2CH_2-, o cicloalquil-$CH_2C(CH_3)_2$-, más preferiblemente cicloalquil-CH_2-. La fracción de alquilo puede estar sustituida, de preferencia mono-sustituida, incluyendo sobre el átomo de carbono en donde se une la fracción de cicloalquilo. Los ejemplos de los sustituyentes preferidos incluyen O-alquilo de 1 a 4 átomos de carbono, tal como OMe, halógeno, hidroxi, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, carboxilo, y ciano, más preferiblemente O-alquilo de 1 a 4 átomos de carbono o hidroxi. Los ejemplos preferidos para la fracción de cicloalquilo son los anillos monocíclicos, de preferencia cicloalquilo de 3 a 7 átomos de carbono, más preferiblemente cicloalquilo de 3, 5, y 6 átomos de carbono. La fracción de cicloalquilo puede estar sustituida o insustituida. Ciclo-alquilo de 3 átomos de carbono de preferencia está insustituido, y cicloalquilo de 5 y 6 átomos de carbono de preferencia está insustituido o sustituido. Cuando la fracción de cicloalquilo está sustituida, de preferencia está mono-sustituida. Los sustituyentes adecuados para la fracción de cicloalquilo son como se definen en la presente, de preferencia O-alquilo de 1 a 4 átomos de carbono, tal como OMe, halógeno, hidroxi, fenilo insustituido o sustituido, naftilo, fenil- o naftil-oxilo insustituido o

sustituido, de preferencia insustituido, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono-amino, tal como -NHCOMe, -NHCOEt, ó $-NHCOCH(CH_3)_2$, carboxilo, y ciano, más preferiblemente amino, O-alquilo de 1 a 4 átomos de carbono, o hidroxi.

(h) Alquiloxi-carbonilo insustituido o sustituido.

Los ejemplos preferidos para la fracción de alquilo son alquilo de 1 a 7 átomos de carbono de cadena ramificada o recta, el cual puede estar sustituido o insustituido. En una modalidad, la fracción de alquilo es alquilo ramificado, tal como isopropilo, isobutilo, butilo secundario o butilo terciario, isopentilo, 1-etil-propilo, 2,2-dimetil-propilo, y 1,2-dimetil-propilo, más preferiblemente isobutilo, isopentilo, y 2,2-dimetil-propilo. En otra modalidad, la fracción de alquilo es alquilo de cadena recta, tal como metilo, etilo, propilo normal, butilo normal, o pentilo normal, de preferencia metilo o etilo. Cuando la fracción de alquilo está sustituida, de preferencia está mono-, di-, o tri-sustituida, más preferible-mente mono-sustituida. Los sustituyentes adecuados para la fracción de alquilo son como se definen en la presente, de preferencia O-alquilo de 1 a 4 átomos de carbono, tal como OMe, halógeno, hidroxi, fenil- o naftil-oxilo insustituido o sustituido, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, nitro, amino, amino-alquilo

de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono-amino, tal como -NHCOMe, amino-carbonilo, amino-carbonilo N-mono- o N,N-di-sustituido, tal como CONHMe, carboxilo, alquiloxilo de 1 a 7 átomos de carbono-carbonilo, tal como COOMe, y ciano, en donde los sustituyentes de fenilo o naftilo adecuados incluyen alquilo de 1 a 7 átomos de carbono, tal como metilo, -O-alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, halógeno, hidroxi, y amino, de preferencia alquilo de 1 a 7 átomos de carbono, y en donde los sustituyentes de amino adecuados incluyen alquilo de 1 a 7 átomos de carbono, tal como metilo, fenilo, o ciclopropilo, de preferencia alquilo de 1 a 7 átomos de carbono. De una manera muy preferible, la fracción de alquilo está mono-sustituida por -O-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono-amino, y amino-carbonilo N-mono- o N,N-di-sustituido.

(i) Arilo mono- o bi-cíclico-oxicarbonilo insustituido o sustituido.

Los ejemplos preferidos de la fracción de arilo incluyen arilo mono- o bi-cíclico con 6 a 22 átomos de carbono, en donde uno de los anillos del arilo bi-cíclico puede ser un anillo parcial o completamente saturado condensado al otro anillo aromático, en especial fenilo, indanilo, indenilo, 1,2,3,4-tetrahidro-naftilo, o naftilo, más preferiblemente fenilo o naftilo. Cuando la fracción de arilo está sustituida, de preferencia está mono- o di-sustituida. En particular, fenilo está de preferencia insustituido, mono- o di-

sustituido, y naftilo está de preferencia insustituido. Los sustituyentes adecuados son como se definen en la presente, de preferencia alquilo de 1 a 7 átomos de carbono, -O-alquilo de 1 a 7 átomos de carbono, tal como OMe, halo-alquilo de 1 a 7 átomos de carbono, halógeno, tal como Cl, -O-alquileno de 1 a 7 átomos de carbono-O-alquilo, tal como O-$C_3H_6OCH_3$, hidroxi, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, carboxilo, y ciano, heterociclilo insustituido o sustituido, de preferencia insustituido, o heterociclil-alquilo de 1 a 4 átomos de carbono insustituido o sustituido, de preferencia insustituido, tal como heterociclil-CH_2, en donde la fracción de heterociclilo en cada caso es de preferencia heterociclilo monocíclico de 5 ó 6 miembros, que preferible-mente contiene un átomo de N y/u O, tal como tetrahidro-furanilo, tetrahidro-piranilo, piperidinilo, pirrolidinilo, pirrolidin-2-onilo, piperazinilo, o morfolinilo, más preferible-mente heterociclilo u -O-alquilo de 1 a 7 átomos de carbono.

(j) Heterociclilo mono- o bi-cíclico-oxicarbonilo insustituido o sustituido.

Los ejemplos preferidos para la fracción de hetero-ciclilo son los anillos mono- o bi-cíclicos. Se prefieren los sistemas de anillo de 3 a 14, más preferiblemente de 5 a 11 miembros. La fracción de heterociclilo puede ser saturada, parcialmente

saturada, o aromática, en particular si se contempla una fracción mono-cíclica, anillos aromáticos o saturados, más preferiblemente saturados, o en particular si se contempla una fracción bi-cíclica, sistemas de anillo aromáticos o parcialmente saturados, en particular en donde uno de los anillos es aromático y el otro está saturado o parcialmente saturado. La fracción de heterociclilo de preferencia tiene 1, 2, ó 3, más preferiblemente 1 ó 2 heteroátomos seleccionados a partir de O, N, o S, más preferiblemente O ó N. Los ejemplos particularmente preferidos incluyen los anillos de 5 ó 6 miembros que de preferencia contienen un átomo de nitrógeno y un átomo de oxígeno, en particular pirrolidinilo, oxazolilo, pirrolidin-2-onilo, pirrolilo, piperidilo, furanilo, pirimidilo, piridilo, pirazinilo, isoxazolilo, pirrolidin-2-onilo, tetrahidro-furanilo, o tetrahidro-piranilo; de una manera más preferible tetra-hidro-furanilo o tetrahidro-piranilo. Cuando la fracción de heterociclilo está sustituida, de preferencia está mono-sustituida. Los sustituyentes adecuados para la fracción de heterociclilo son como se definen en la presente, de preferencia -alquilo de 1 a 7 átomos de carbono, tal como metilo, halógeno, hidroxi, alcanoílo de 1 a 7 átomos de carbono, fenilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, cicloalquilo de 3 a 8 átomos de carbono insustituido o sustituido, de preferencia insustituido, tal como

ciclopropilo, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, carboxilo, y ciano, muy preferiblemente fenilo, -alquilo de 1 a 7 átomos de carbono, o cicloalquilo de 3 a 8 átomos de carbono. Los sustituyentes de fenilo y ciclo-alquilo adecuados incluyen alquilo de 1 a 7 átomos de carbono, -O-alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, halógeno, hidroxi, y amino. De una manera muy preferible, la fracción de heterociclilo está insustituida.

(k) Cicloalquilo mono- o bi-cíclico-oxicarbonilo insustituido o sustituido.

Los ejemplos preferidos para la fracción de ciclo-alquilo son los anillos mono-cíclicos, de preferencia ciclo-alquilo de 3 a 8 átomos de carbono, más preferiblemente cicloalquilo de 3, 4, 5, 6, y 7 átomos de carbono, de una manera muy preferible cicloalquilo de 6 átomos de carbono. La fracción de cicloalquilo puede estar sustituida o insustituida, de preferencia insustituida. Cuando la fracción de cicloalquilo está sustituida, de preferencia está mono-sustituida. Los sustituyentes adecuados para la fracción de cicloalquilo son como se definen en la presente, de preferencia O-alquilo de 1 a 4 átomos de carbono, tal como OMe, halógeno, hidroxi, fenilo insustituido o sustituido, naftilo, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono-amino,

carboxilo, y ciano, más preferiblemente O-alquilo de 1 a 4 átomos de carbono o hidroxi.

(l) Arilo mono- o bi-cíclico-alquiloxilo de 1 a 7 átomos de carbono-carbonilo insustituido o sustituido.

De preferencia, aril-alquilo es aril-alquilo de 1 a 6 átomos de carbono, más preferiblemente aril-alquilo de 1 a 4 átomos de carbono, en particular aril-CH_2-, aril-CH_2CH_2-, aril-$CH(CH_3)$-, aril-$CH_2CH(CH_3)$-, o aril-$CH(CH_2CH_3)$-, de una manera más preferible aril-CH_2-. Los ejemplos preferidos de la fracción de arilo incluyen arilo mono- o bi-cíclico con 6 a 22 átomos de carbono, en donde uno de los anillos del arilo bicíclico puede ser un anillo parcial o completamente saturado condensado al otro anillo aromático, en especial fenilo, indanilo, indenilo, 1,2,3,4-tetrahidro-naftilo, o naftilo, más preferiblemente fenilo. Cuando la fracción de arilo está sustituida, de preferencia está mono-, di-, o tri-sustituida. En una modalidad, el fenilo de preferencia está insustituido. Los sustituyentes adecuados son como se definen en la presente, de preferencia alquilo de 1 a 7 átomos de carbono, -O-alquilo de 1 a 7 átomos de carbono, tal como OMe, halo-alquilo de 1 a 7 átomos de carbono, tal como CF_3, halógeno, tal como Cl ó F, -O-alquileno de 1 a 7 átomos de carbono-O-alquilo, tal como O-$C_3H_6OCH_3$, hidroxi, fenilo o naftilo insustituido o sustituido, de preferencia sustituido, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, nitro, amino,

amino-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono-amino, tal como -NHCOMe, carboxilo, y ciano. Los sustituyentes adecuados para el sustituyente de fenilo y naftilo sobre la fracción de arilo del aril-alquil-carbonilo incluyen alquilo de 1 a 7 átomos de carbono, -O-alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, halógeno, hidroxi, y amino.

(m) Heterociclilo mono- o bi-cíclico-alquiloxilo de 1 a 7 átomos de carbono-carbonilo insustituido o sustituido.

De preferencia, heterociclil-alquilo es heterociclil-alquilo de 1 a 6 átomos de carbono, más preferiblemente heterociclil-alquilo de 1 a 4 átomos de carbono, en particular heterociclil-CH_2-, heterociclil-CH_2CH_2-, o heterociclil-$CH_2CH(CH_3)$-, más preferiblemente heterociclil-CH_2-. Se prefiere en particular heterociclil-$CH_2CH(CH_3)$- cuando la fracción de heterociclilo es un anillo de 5 ó 6 miembros, tal como un anillo saturado, en particular 1,3-dioxano. Los ejemplos preferidos para la fracción de heterociclilo son los anillos mono- o bi-cíclicos.

Se prefieren los sistemas de anillo de 3 a 14, más preferiblemente de 5 a 11 miembros. La fracción de hetero-ciclilo puede ser saturada, parcialmente saturada, o aromática, en particular si se contempla una fracción mono-cíclica, anillos aromáticos o saturados, o en particular si se contempla una fracción bicíclica, sistemas de anillo aromáticos o parcialmente saturados, en particular en donde uno de los anillos es aromático y

el otro está saturado o parcialmente saturado. La fracción de heterociclilo tiene de preferencia 1,2, ó 3, más preferiblemente 1 ó 2 heteroátomos seleccionados a partir de O, N, ó S, más preferiblemente O ó N. Los ejemplos particularmente preferidos incluyen los anillos de 5 ó 6 miembros que de preferencia contienen un átomo de nitrógeno o un átomo de oxígeno, en particular pirrolidinilo, oxazolilo, pirimidilo, piridilo, pirazinilo, isoxazolilo, pirrolidin-2-onilo, pirrolilo, piperidilo, furanilo, 1,3-dioxano, tetrahidro-furanilo, o tetrahidro-piranilo; de una manera más preferible piridilo, piperidilo, isoxazolilo, tetra-hidrofuranilo, tetrahidropiranilo, o 1,3-dioxano. Cuando la fracción de heterociclilo está sustituida, de preferencia está mono-sustituida. Los sustituyentes adecuados para la fracción de heterociclilo son como se definen en la presente, de preferencia -alquilo de 1 a 7 átomos de carbono, tal como metilo, halógeno, hidroxi, alcanoílo de 1 a 7 átomos de carbono, tal como COMe, fenilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, cicloalquilo de 3 a 8 átomos de carbono insustituido o sustituido, de preferencia insustituido, tal como ciclopropilo, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, carboxilo, y ciano, más preferiblemente -alquilo de 1 a 7 átomos de carbono o alcanoílo de 1 a 7 átomos de carbono. Los sustituyentes de fenilo y cicloalquilo adecuados incluyen alquilo de

1 a 7 átomos de carbono, -O-alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, halógeno, hidroxi, y amino. De una manera muy preferible, la fracción de heterociclilo está insustituida o está mono-sustituida con -alquilo de 1 a 7 átomos de carbono o alcanoílo de 1 a 7 átomos de carbono.

(n) Cicloalquilo mono- o bi-cíclico-alquiloxilo de 1 a 7 átomos de carbono-carbonilo insustituido o sustituido.

De preferencia, cicloalquil-alquilo es cicloalquil-alquilo de 1 a 6 átomos de carbono, más preferiblemente cicloalquil-alquilo de 1 a 4 átomos de carbono, en particular cicloalquil-CH_2-, cicloalquil-CH_2CH_2-, o cicloalquil-$CH_2CH(CH_3)$-, más preferiblemente cicloalquil-CH_2-. Los ejemplos preferidos para la fracción de cicloalquilo son los anillos monocíclicos, de preferencia cicloalquilo de 3 a 7 átomos de carbono, más preferiblemente cicloalquilo de 3 y 5 átomos de carbono. La fracción de cicloalquilo puede estar sustituida o insustituida. Ciclo-alquilo de 3 átomos de carbono de preferencia está insustituido, y cicloalquilo de 5 átomos de carbono de preferencia está insustituido o sustituido. Cuando la fracción de cicloalquilo está sustituida, de preferencia está mono-sustituida. Los sustituyentes adecuados para la fracción de cicloalquilo son como se definen en la presente, de preferencia O-alquilo de 1 a 4 átomos de carbono, tal como OMe, halógeno, hidroxi, fenilo insustituido o sustituido, naftilo, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, de

preferencia insustituido, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono-amino, tal como -NHCOMe, -NHCOEt, ó -$NHCOCH(CH_3)_2$, carboxilo, y ciano, más preferiblemente alcanoílo de 1 a 7 átomos de carbono-amino.

(o) N-mono- o N,N-di-(arilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, y/o alquilo insustituido o sustituido)-amino-carbonilo.

Los ejemplos preferidos para la fracción de alquilo del alquil-amino-carbonilo insustituido o sustituido son alquilo de 1 a 7 átomos de carbono de cadena ramificada o recta, el cual puede estar sustituido o insustituido. En una modalidad, la fracción de alquilo es alquilo ramificado, tal como isopropilo, isobutilo, butilo secundario o butilo terciario, isopentilo, 1-etil-propilo, 2,2-dimetil-propilo, y 1,2-dimetil-propilo, más preferiblemente isopropilo o isobutilo. En otra modalidad, la fracción de alquilo es alquilo de cadena recta, tal como metilo, etilo, propilo normal, butilo normal, o pentilo normal, de preferencia metilo o etilo. Cuando la fracción de alquilo está sustituida, de preferencia está mono-, di-, o tri-

sustituida, más preferiblemente mono-sustituida. Los sustituyentes adecuados para la fracción de alquilo son como se definen en la presente, de preferencia O-alquilo de 1 a 4 átomos de carbono, tal como OMe, halógeno, hidroxi, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil- alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono-amino, tal como -NHCOMe, amino-carbonilo, amino-carbonilo N-mono- o N,N-di-sustituido, tal como CONHMe, carboxilo, alquiloxilo de 1 a 7 átomos de carbono-carbonilo, tal como COOMe, y ciano. De una manera muy preferible, la fracción de alquilo está insustituida.

Los ejemplos preferidos de la fracción de arilo del aril-amino-carbonilo insustituido o sustituido incluyen arilo mono- o bi-cíclico con 6 a 22 átomos de carbono, en donde uno de los anillos del arilo bicíclico puede ser un anillo parcial o completamente saturado condensado al otro anillo aromático, en especial fenilo, indanilo, indenilo, 1,2,3,4-tetrahidro-naftilo, o naftilo, más preferiblemente fenilo o naftilo. Cuando la fracción de arilo está sustituida, de preferencia está mono- o di-sustituida. Los sustituyentes adecuados son como se definen en la presente, de preferencia alquilo de 1 a 7 átomos de carbono, -O-alquilo de 1 a 7 átomos de carbono, tal como OMe, halo-alquilo de 1 a 7 átomos de carbono, tal como Cl, -O-alquileno de 1 a 7 átomos de carbono-O-alquilo, tal como $O\text{-}C_3H_6OCH_3$, hidroxi, fenil- o naftil-oxilo

insustituido o sustituido, de preferencia insustituido, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, carboxilo, y ciano. De una manera muy preferible, arilo está insustituido.

Los ejemplos preferidos para la fracción de ciclo-alquilo del cicloalquil-amino-carbonilo insustituido o sustituido son los anillos monocíclicos, de preferencia ciclo-alquilo de 3 a 8 átomos de carbono, más preferiblemente cicloalquilo de 3, 4, 5, 6, y 7 átomos de carbono, de una manera muy preferible cicloalquilo de 3 a 6 átomos de carbono. La fracción de cicloalquilo puede estar sustituida o insustituida, de preferencia insustituida. Cuando la fracción de cicloalquilo está sustituida, de preferencia está mono-sustituida. Los sustituyentes adecuados para la fracción de cicloalquilo son como se definen en la presente, de preferencia O-alquilo de 1 a 4 átomos de carbono, tal como OMe, halógeno, hidroxi, fenilo insustituido o sustituido, naftilo, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono-amino, carboxilo, y ciano, más preferiblemente O-alquilo de 1 a 4 átomos de carbono o hidroxi.

De una manera preferible, la fracción de aril-alquilo del aril-alquil-amino-carbonilo insustituido o sustituido es aril-alquilo de 1

a 6 átomos de carbono, más preferiblemente aril-alquilo de 1 a 4 átomos de carbono, en particular aril-CH_2-, aril-CH_2CH_2-, o aril-$CH(CH_2CH_3)$-, y de una forma muy preferible aril-CH_2-. La fracción de alquilo, en particular cuando el aril-alquilo es aril-CH_2-, puede estar sustituida, de preferencia mono-sustituida. Los ejemplos de los sustituyentes preferidos incluyen O-alquilo de 1 a 4 átomos de carbono, tal como OMe, halógeno, hidroxi, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono-amino, tal como -NHCOMe, carboxilo, y ciano, o fenilo insustituido o sustituido, de preferencia insustituido, en donde los sustituyentes de fenilo adecuados incluyen alquilo de 1 a 7 átomos de carbono, -O-alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, halógeno, hidroxi, y amino; se prefiere más fenilo insustituido. Los ejemplos preferidos de la fracción de arilo incluyen arilo mono- o bi-cíclico con 6 a 22 átomos de carbono, en donde uno de los anillos del arilo bi-cíclico puede ser un anillo parcial o completamente saturado condensado al otro anillo aromático, en especial fenilo, indanilo, indenilo, 1,2,3,4-tetrahidronaftilo, o naftilo, más preferiblemente fenilo. Cuando la fracción de arilo está sustituida, de preferencia está mono-, di-, o tri-sustituida. En una modalidad, el fenilo de preferencia está insustituido. Los sustituyentes adecuados son como se definen en la presente, de preferencia alquilo de 1 a 7 átomos de carbono, -O-alquilo de 1 a 7 átomos de carbono, tal como OMe, halo-alquilo de 1 a 7 átomos de carbono, tal como CF_3, halógeno, tal como Cl ó

F, -O-alquileno de 1 a 7 átomos de carbono-O-alquilo, tal como O-$C_3H_6OCH_3$, hidroxi, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono-amino, tal como -NHCOMe, carboxilo, y ciano, más preferiblemente -O-alquilo de 1 a 7 átomos de carbono, o halógeno.

De preferencia, la fracción de heterociclil-alquilo del heterociclil-alquil-amino-carbonilo insustituido o sustituido es heterociclil-alquilo de 1 a 6 átomos de carbono, más preferiblemente heterociclil-alquilo de 1 a 4 átomos de carbono, en particular heterociclil-CH_2- o heterociclil-CH_2CH_2-, y de una manera muy preferible heterociclil-CH_2-. Los ejemplos preferidos para la fracción de heterociclilo son los anillos mono- o bi-cíclicos. Se prefieren los sistemas de anillo de 3 a 14, más preferiblemente de 5 a 11 miembros. La fracción de heterociclilo puede ser saturada, parcialmente saturada, o aromática, en particular si se contempla una fracción monocíclica, anillos aromáticos o saturados, o en particular si se contempla una fracción bicíclica, sistemas de anillo aromáticos o parcialmente saturados, en particular en donde uno de los anillos es aromático y el otro está saturado o parcialmente saturado. La fracción de heterociclilo tiene de preferencia 1, 2, ó 3, más preferiblemente 1 ó 2 hetero-átomos seleccionados a partir de O, N, ó S, más preferible-mente O ó N. Los ejemplos particularmente preferidos incluyen anillos de 5 ó 6 miembros que de preferencia contienen un átomo de nitrógeno o un átomo de oxígeno, en particular pirrolidinilo,

oxazolilo, pirimidilo, piridilo, pirazinilo, isoxazolilo, pirrolidin-2-onilo, pirrolilo, piperidilo, furanilo, 1,3-dioxano, tetrahidro-furanilo, o tetrahidro-piranilo; de una manera más preferible, furanilo o tetrahidro-piranilo. Cuando la fracción de heterociclilo está sustituida, de preferencia está mono-sustituida. Los sustituyentes adecuados para la fracción de heterociclilo son como se definen en la presente, de preferencia -alquilo de 1 a 7 átomos de carbono, tal como metilo, halógeno, hidroxi, alcanoílo de 1 a 7 átomos de carbono, tal como COMe, fenilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, cicloalquilo de 3 a 8 átomos de carbono insustituido o sustituido, de preferencia insustituido, tal como ciclopropilo, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, carboxilo, y ciano, más preferiblemente alquilo de 1 a 7 átomos de carbono o alcanoílo de 1 a 7 átomos de carbono. Los sustituyentes de fenilo y cicloalquilo adecuados incluyen alquilo de 1 a 7 átomos de carbono, -O-alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, halógeno, hidroxi, y amino. De una manera muy preferible, la fracción de heterociclilo está insustituida.

De una manera preferible, la fracción de ciclo-alquil-alquilo del cicloalquil-alquil-amino-carbonilo insustituido o sustituido es cicloalquil-alquilo de 1 a 6 átomos de carbono, más preferiblemente cicloalquil-alquilo de 1 a 4 átomos de carbono, en

particular cicloalquil-CH_2-. Los ejemplos preferidos para la fracción de cicloalquilo son los anillos monocíclicos, de preferencia cicloalquilo de 3 a 7 átomos de carbono, más preferiblemente cicloalquilo de 6 átomos de carbono. La fracción de cicloalquilo puede estar sustituida o insustituida, de preferencia insustituida. Cuando la fracción de cicloalquilo está sustituida, de preferencia está mono-sustituida. Los sustituyentes adecuados para la fracción de cicloalquilo son como se definen en la presente, de preferencia O-alquilo de 1 a 4 átomos de carbono, tal como OMe, halógeno, hidroxi, fenilo insustituido o sustituido, naftilo, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono-amino, tal como -NHCOMe, -NHCOEt, ó -$NHCOCH(CH_3)_2$, carboxilo, y ciano, más preferiblemente alcanoílo de 1 a 7 átomos de carbono-amino.

Los ejemplos preferidos de N-mono- o N,N-di-(arilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido-alquilo de 1 a 7 átomos de carbono, cicloalquilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, y/o alquilo insustituido o sustituido)-amino-carbonilo, incluyen:

(arilo mono- o bi-cíclico insustituido o sustituido)-(alquilo insustituido o sustituido)-amino-carbonilo,

heterociclilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono-amino-carbonilo insustituido o sustituido,

arilo mono- o bi-cíclico-amino-carbonilo insustituido o sustituido,

cicloalquilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono-amino-carbonilo insustituido o sustituido,

di-(arilo mono- o bi-cíclico insustituido o sustituido)-amino-carbonilo,

di-(alquilo insustituido o sustituido)-amino-carbonilo,

(arilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido)-(alquilo insustituido o sustituido)-amino-carbonilo,

(cicloalquilo mono- o bi-cíclico insustituido o sustituido)-(arilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido)-amino-carbonilo,

cicloalquilo mono- o bi-cíclico insustituido o sustituido)-(arilo mono- o bi-cíclico insustituido o sustituido)-amino-carbonilo, y

cicloalquilo mono- o bi-cíclico-amino-carbonilo insustituido o sustituido.

(p) Arilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono-sulfonilo insustituido o sustituido.

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De preferencia, aril-alquilo es aril-alquilo de 1 a 6 átomos de carbono, más preferiblemente aril-alquilo de 1 a 4 átomos de carbono, en particular aril-CH_2-, aril-CH_2CH_2- aril-$CH(CH_3)$-, aril-$CH_2CH(CH_3)$-, o aril-$CH(CH_2CH_3)$-, más preferiblemente aril-CH_2-. Los ejemplos preferidos de la fracción de arilo incluyen arilo mono- o bicíclico con 6 a 22 átomos de carbono, en donde uno de los anillos del arilo bi-cíclico puede ser un anillo parcial o completamente saturado condensado al otro anillo aromático, en especial fenilo, indanilo, indenilo, 1,2,3,4-tetrahidronaftilo, o naftilo, más preferiblemente fenilo. Cuando la fracción de arilo está sustituida, de preferencia está mono-, di-, o tri-sustituida. En una modalidad, el fenilo de preferencia está insustituido. Los sustituyentes adecuados son como se definen en la presente, de preferencia alquilo de 1 a 7 átomos de carbono, -O-alquilo de 1 a 7 átomos de carbono, tal como OMe, halo-alquilo de 1 a 7 átomos de carbono, tal como CF_3, halógeno, tal como Cl ó F, -O-alquileno de 1 a 7 átomos de carbono-O-alquilo, tal como O-$C_3H_6OCH_3$, hidroxi, fenilo o naftilo insustituido o sustituido, de preferencia sustituido, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono-amino, tal como -NHCOMe, carboxilo, y ciano. Los sustituyentes adecuados para el sustituyente de fenilo y naftilo sobre la fracción de arilo del aril-alquil-carbonilo incluyen

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alquilo de 1 a 7 átomos de carbono, -O-alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, halógeno, hidroxi, y amino.

Cuando R_b es acilo, R_c es como se define en la presente, de preferencia R_c es hidroxi-alquilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, o de preferencia hidrógeno, ciclo-alquilo de 3 a 8 átomos de carbono insustituido o sustituido, o alquilo de 1 a 7 átomos de carbono insustituido o sustituido, más preferiblemente ciclopropilo o metilo. En particular, cuando R_b es acilo como se define en (h) a (n), R_c es de preferencia hidrógeno, cicloalquilo de 3 a 8 átomos de carbono insustituido o sustituido, o alquilo de 1 a 7 átomos de carbono insustituido o sustituido, más preferiblemente ciclopropilo o metilo. En particular, cuando R_b es acilo como se define en (o), R_c es de preferencia cicloalquilo de 3 a 8 átomos de carbono insustituido o sustituido, más preferible-mente ciclopropilo. En particular, cuando R_b es acilo como se define en (p), R_c es de preferencia cicloalquilo de 3 a 8 átomos de carbono insustituido o sustituido, más preferible-mente metilo o isobutilo.

Cuando R_c es hidrógeno, entonces uno o más, de preferencia todos los siguientes sustituyentes, tienen la siguiente definición:

R_b es arilo insustituido o sustituido como se define en la

presente, de preferencia fenilo insustituido, aril-alquil-carbonilo insustituido o sustituido como se define en la presente, de preferencia fenil-$C(CH_3)_2$-CO insustituido o fenil-CH(OMe)-CO insustituido, o aril-carbonilo insustituido o sustituido como se define en la presente, de preferencia indanil-CO- insustituido, heterociclil-carbonilo insustituido o sustituido como se define en la presente, de preferencia 2,3-dihidro-benzo[1,4]dioxinil-CO- insustituido, heterociclil-alquil-carbonilo insustituido o sustituido como se define en la presente, y de una manera preferible, tetrahidropiranil-CH_2-CO- insustituido;

R^1 es fenil-carbonilo sustituido como se define en la presente, en particular en donde un sustituyente es -O-alquilo de 1 a 7 átomos de carbono, tal como OMe, o -alquilo de 1 a 7 átomos de carbono, tal como metilo o etilo, y el otro es -O-alquileno de 1 a 7 átomos de carbono-O-alquilo de 1 a 7 átomos de carbono, tal como $-OC_3H_6OMe$;

R^2 es alquilo ramificado, tal como isopropilo;

T es metileno, y

R^4 y R^5 son hidrógeno.

Cuando R_c es alquilo de 1 a 7 átomos de carbono insustituido o sustituido, los ejemplos preferidos son alquilo de 1 a 7 átomos de carbono de cadena ramificada o recta, el cual puede estar sustituido o insustituido. En una modalidad preferida, R_c es alquilo ramificado, tal como isopropilo, iso-butilo, butilo secundario o butilo terciario, isopentilo, 1-etil-propilo, y 1,2-

dimetil-propilo, más preferiblemente isopropilo. En otra modalidad preferida, R_c es alquilo de cadena recta, tal como metilo, etilo, propilo normal, butilo normal o pentilo normal, más preferiblemente metilo o etilo, y de una manera muy preferible etilo. Si la fracción de alquilo está sustituida, los sustituyentes adecuados con como se definen en la presente, de preferencia O-alquilo de 1 a 4 átomos de carbono, halógeno, hidroxi, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, carboxilo, y ciano. De una forma muy preferible, la fracción de alquilo está insustituida.

Cuando R_c es cicloalquilo de 3 a 8 átomos de carbono insustituido o sustituido, los ejemplos preferidos para la fracción de cicloalquilo son anillos monocíclicos, de preferencia cicloalquilo de 3 a 7 átomos de carbono, más preferiblemente cicloalquilo de 3, 4, 5, y 6 átomos de carbono, de una manera más preferible ciclopropilo o ciclo-butilo, y muy preferiblemente ciclopropilo. La fracción de cicloalquilo puede estar sustituida o insustituida. Cuando la fracción de cicloalquilo está sustituida, de preferencia está mono-sustituida. Los sustituyentes adecuados para la fracción de cicloalquilo son como se definen en la presente, de preferencia O-alquilo de 1 a 4 átomos de carbono, halógeno, hidroxi, fenilo insustituido o sustituido, naftilo, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-alquiloxilo de

1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, carboxilo, y ciano, más preferiblemente fenilo o naftilo. De una forma muy preferible, la fracción de cicloalquilo está insustituida.

Cuando R_c es cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, tal como cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 4 átomos de carbono, en particular ciclo-alquilo de 3 a 8 átomos de carbono-CH_2, los ejemplos preferidos para la fracción de cicloalquilo son los anillos monocíclicos, de preferencia cicloalquilo de 3 a 7 átomos de carbono, más preferiblemente cicloalquilo de 3, 4, 5, y 6 átomos de carbono, y muy preferiblemente ciclopropilo. La fracción de cicloalquilo puede estar sustituida o insustituida. Cuando la fracción de cicloalquilo está sustituida, de preferencia está mono-sustituida. Los sustituyentes adecuados para la fracción de cicloalquilo son como se definen en la presente, de preferencia O-alquilo de 1 a 4 átomos de carbono, halógeno, hidroxi, fenilo insustituido o sustituido, naftilo, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, carboxilo, y ciano, más preferiblemente fenilo o naftilo. De una forma muy preferible, la fracción de cicloalquilo está insustituida.

Cuando R_c es cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono insustituida o sustituida, entonces uno o más de, preferiblemente todos, los siguientes sustituyentes tienen la siguiente definición:

R^1 es fenil-carbonilo sustituido como se define en la presente, en particular en donde un sustituyente es -O-alquilo de 1 a 7 átomos de carbono, tal como OMe, o -alquilo de 1 a 7 átomos de carbono, tal como metilo o etilo, y el otro es -O-alquileno de 1 a 7 átomos de carbono-O-alquilo de 1 a 7 átomos de carbono, tal como $-O-C_3H_6OMe$;

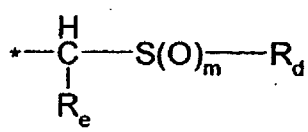
R^2 es alquilo ramificado, tal como isopropilo;

T es metileno, y

R^4 y R^5 son hidrógeno.

Cuando R^3 es una fracción de la Fórmula (b), R_e es como se define en la presente, de preferencia R_e es hidrógeno.

R^3 es, en una tercera modalidad, una fracción de la Fórmula (c):

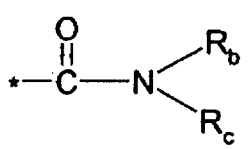


En esta modalidad, R_d es como se define en la presente, en particular R_d es fenil- o naftil-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, en donde, en el caso de una fracción sustituida, los sustituyentes son uno o más, en especial hasta tres sustituyentes independientemente seleccionados a partir de

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aquéllos mencionados para fenil- o naftil-alquilo de 1 a 7 átomos de carbono insustituido o sustituido bajo R_b, o es $-N(R_b)(R_c)$, en donde R_b y R_c son como se definen para la segunda modalidad anterior, de preferencia es (fenil- o naftil)-alquilo de 1 a 7 átomos de carbono insustituido o sustituido por [alquilo de 1 a 7 átomos de carbono, fenilo, halo-alquilo inferior, halógeno, oxo-alquilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono, fenil-alcoxilo de 1 a 7 átomos de carbono, halo-alquiloxilo de 1 a 7 átomos de carbono, fenoxilo, alcanoílo de 1 a 7 átomos de carbono-amino, ciano, alcanoílo de 1 a 7 átomos de carbono, y/o alquilo de 1 a 7 átomos de carbono-sulfonilo]; más preferiblemente bencilo.

En una cuarta modalidad, R^3 es una fracción de la Fórmula (f):



En esta modalidad, R_b es como se define en la presente, en particular como se describe con respecto a la segunda modalidad en donde R^3 es una fracción de la Fórmula (b). De preferencia, R_b es aril-alquilo, tal como fenil-alquilo de 1 a 4 átomos de carbono, en donde la fracción de arilo está insustituida o sustituida por un sustituyente adecuado, tal como alquilo de 1 a 7 átomos de carbono, -O-alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, halógeno, hidroxi, fenil- o naftil-oxilo,

fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, carboxilo, y ciano; de preferencia, la fracción de arilo está insustituida. O R_b es alquilo insustituido o sustituido. Los ejemplos preferidos son alquilo de 1 a 7 átomos de carbono de cadena ramificada o recta, el cual puede estar sustituido o insustituido, de preferencia alquilo de cadena recta tal como metilo, etilo, propilo normal, butilo normal o pentilo normal, de preferencia metilo, en donde la fracción de alquilo está insustituida o sustituida por un sustituyente adecuado, tal como O-alquilo de 1 a 4 átomos de carbono, halógeno, hidroxi, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, carboxilo, y ciano; de preferencia, la fracción de alquilo está insustituida.

En esta modalidad, R_c es como se define en la presente, de preferencia R_c es hidrógeno.

Cuando R^3 es una fracción de la Fórmula (f), entonces uno o más de, preferiblemente todos, los siguientes sustituyentes tienen la siguiente definición:

R^1 es fenil-carbonilo sustituido como se define en la presente, en particular en donde un sustituyente es -O-alquilo de 1 a 7 átomos de carbono, tal como OMe, o -alquilo de 1 a 7 átomos de carbono, tal como metilo o etilo, y el otro es -O-alquileno de 1 a 7 átomos de carbono-O-alquilo de 1 a 7 átomos de carbono, tal

como -O-C_3H_6OMe;

R^2 es alquilo ramificado, tal como isopropilo;

T es metileno, y

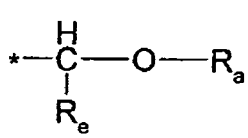
R^4 y R^5 son hidrógeno.

En los Ejemplos se proporcionan las modalidades particulares de la invención, en especial de los compuestos de la Fórmula I, y/o sales de los mismos - y por lo tanto, la invención, en una modalidad muy preferida, se refiere a un compuesto de la Fórmula I, o una sal del mismo, seleccionado a partir de los compuestos dados en los Ejemplos, así como el uso de los mismos.

Proceso de Manufactura

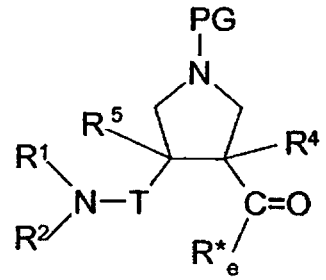
Un compuesto de la Fórmula I, o una sal del mismo, se prepara de una manera análoga a los métodos que, para otros compuestos, son en principio conocidos en la técnica, de tal manera que, para los compuestos novedosos de la Fórmula I, el proceso es novedoso cuando menos como un proceso de analogía, en especial como se describe o en analogía a los métodos descritos en la presente en los Ejemplos ilustrativos, o modificaciones de los mismos, de preferencia en general mediante:

(A) para la síntesis de un compuesto de la Fórmula I, en donde R^3 es una fracción de la Fórmula (a):



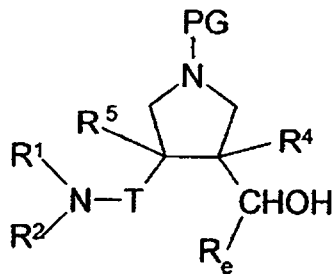
(a)

en donde R_a y R_e son como se definen para un compuesto de la Fórmula I, y R^1, R^2, R^4, R^5, y T son como se definen para un compuesto de la Fórmula I, reducir un compuesto de la Fórmula II:



(II)

en donde R^1, R^2, R^4, R^5, y T son como justamente se definieron, R^*_e es hidroxi, o R_e es como se define para un compuesto de la Fórmula I, y PG es un grupo protector, hasta el compuesto de hidroxi correspondiente de la Fórmula III:



(III)

en donde R_e es como se define para un compuesto de la Fórmula I, y las otras fracciones son como se definen, el cual entonces se desprotege hasta un compuesto correspondiente de la Fórmula I, en donde R_a en la fracción de la Fórmula (a) es hidrógeno, o se hace reaccionar adicionalmente con cualquiera de:

(i) con un compuesto de la Fórmula IV:

$$R_a^*\text{-}X \qquad \text{(IV)}$$

en donde R_a^* es alquilo insustituido o sustituido, arilo

mono- o bi-cíclico insustituido o sustituido, hetero-ciclilo mono- o bi-cíclico insustituido o sustituido, ciclo-alquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, o acilo, y X es un grupo saliente, o

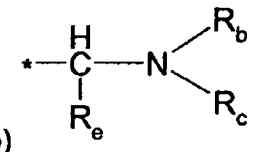
(ii) con el objeto de introducir una fracción R_a que es N-(arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, o alquilo insustituido o sustituido)-amino-carbonilo, con un compuesto de isocianato de la Fórmula IV*:

$$R_a{}^{**}\text{-}N=C=O \qquad (IV^*)$$

en donde R_a es arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, o alquilo insustituido o sustituido,

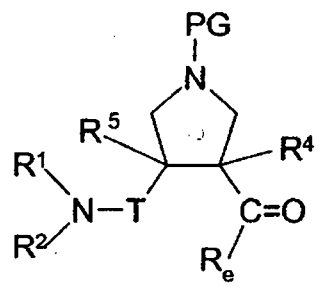
en donde la reacción (i) ó (ii) es seguida por la remoción de cualesquiera grupos protectores, para dar un compuesto correspondiente de la Fórmula I si no se desea una conversión adicional que requiera de la presencia de grupos protectores; o

(B) para la síntesis de un compuesto de la Fórmula I, en donde R^3 es una fracción de la Fórmula (b):



(b)

en donde R_e, R_b, y R_c son como se definen para un compuesto de la Fórmula I, y en donde R^1, R^2, R^4, R^5, y T son como se definen para un compuesto de la Fórmula I, hacer reaccionar un compuesto de aldehído de la Fórmula V:



(V)

en donde R_e, R^1, R^2, R^4, R^5, y T son como se definen para un compuesto de la Fórmula I, y PG es un grupo protector,

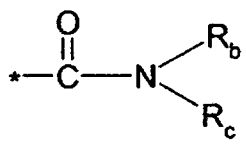
bajo condiciones de aminación reductiva, con un compuesto de la Fórmula VI:

$$R_b\text{-}NH\text{-}R_c \qquad \text{(VI)}$$

en donde R_b y R_c son como se definen para un compuesto de la Fórmula I, seguido por, si no se pretende una conversión

adicional que requiera de grupos protectores, la remoción de cualesquiera grupos protectores; o

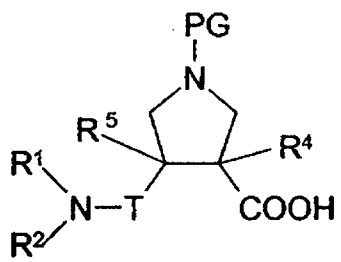
(C) para la síntesis de un compuesto de la Fórmula I, en donde R^3 es una fracción de la Fórmula (f):



(f)

en donde R_b y R_c, así como R^1, R^2, R^4, R^5, y T son como se definen para un compuesto de la Fórmula I,

condensar un ácido de la Fórmula IIB:



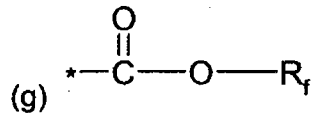
(IIB)

en donde R^1, R^2, R^4, R^5, y T son como se definen para un compuesto de la Fórmula I, y PG es un grupo protector, o un derivado reactivo del mismo, con una amina de la Fórmula VI:

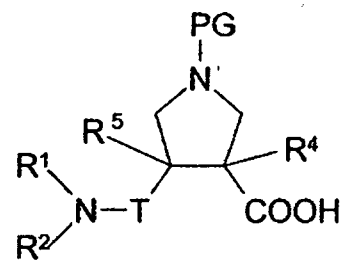
$$R_b\text{-}NH\text{-}R_c \qquad \text{(VI)}$$

en donde R_b y R_c son como se definen para un compuesto de la Fórmula I, seguido por, si no se pretenden una conversión adicional que requiera de grupos protectores, la remoción de cualesquiera grupos protectores; o

(D) para la síntesis de un compuesto de la Fórmula I, en donde R^3 es una fracción de la Fórmula (g):

(g) 

en donde R_f es como se define para un compuesto de la Fórmula I, y en donde R^1, R^2, R^4, R^5, y T son como se definen para un compuesto de la Fórmula I, hacer reaccionar un ácido de la Fórmula IIB:



(IIB)

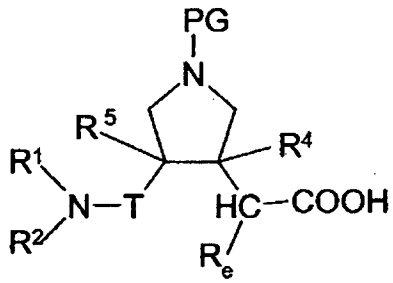
en donde R^1, R^2, R^4, R^5, y T son como se definen para un compuesto de la Fórmula I, y PG es un grupo protector, o un derivado reactivo del mismo, con un alcohol o un derivado de alcohol de la Fórmula VII:

R_f-X **(VII)**

en donde R_f es como se define para un compuesto de la Fórmula I, y X es hidroxi o un grupo saliente, seguido por, si no se pretende una conversión adicional que requiera de grupos protectores, la remoción de cualesquiera grupos protectores; o

(E) para la síntesis de un compuesto de la Fórmula I, en donde R^3 es una fracción de la Fórmula (d) ó (e) como se define para un compuesto de la Fórmula I, y R^1, R^2, R^4, R^5, y T son como se definen para un compuesto de la Fórmula I, hacer reaccionar un

compuesto de la Fórmula IIA:



(IIA)

en donde R^1, R^2, R^4, R^5, T, y R_e son como se definen para un compuesto de la Fórmula I,

(i) para la síntesis de un compuesto de la Fórmula I, en donde R^3 es una fracción de la Fórmula (d), con un compuesto de la Fórmula VI:

$$R_b\text{-}NH\text{-}R_c \qquad \text{(VI)}$$

en donde R_a y R_b son como se definen para un compuesto de la Fórmula I, o

(ii) para la síntesis de un compuesto de la Fórmula I, en donde R^3 es una fracción de la Fórmula (e), con un compuesto de la Fórmula VII:

$$R_f\text{-}X \qquad \text{(VII)}$$

en donde R_f es como se define para un compuesto de la Fórmula I, y X es hidroxi o un grupo saliente;

y, si se desea, subsecuentemente a cualquiera o más de los procesos (A), (B), (C), (D), o (E) mencionados anteriormente, convertir un compuesto que se pueda obtener de la Fórmula I, o una forma protegida del mismo, en un compuesto diferente de la Fórmula I, convertir una sal de un compuesto que se pueda

obtener de la Fórmula I en el compuesto libre o en una sal diferente, convertir un compuesto libre que se pueda obtener de la Fórmula I en una sal del mismo, y/o separar una mezcla que se pueda obtener de isómeros de un compuesto de la Fórmula I, en los isómeros individuales;

en donde, en cualquiera de los materiales de partida (en especial de las fórmulas II, IIA, IIB, III, IV, IV*, V, VI, y VII), en adición a los grupos protectores específicos mencionados, puede haber grupos protectores adicionales presentes, y cualesquiera grupos protectores se retiran en una etapa apropiada con el objeto de obtener un compuesto correspondiente de la Fórmula I, o una sal del mismo.

Condiciones de Reacción Preferidas

Las condiciones de reacción preferidas para las reacciones mencionadas anteriormente, así como para las transformaciones y conversiones, son como sigue (o análogas a los métodos empleados en los Ejemplos o como se describe en los mismos):

La reducción según (A) de preferencia tiene lugar bajo las condiciones acostumbradas para la reducción de ácidos carbónicos hasta los alcoholes correspondientes, de preferencia en la presencia de un hidruro complejo apropiado, tal como un complejo de borano-sulfuro de dimetilo, en un solvente apropiado, por ejemplo un éter, tal como tetrahidrofurano, a temperaturas preferidas, por ejemplo, de -40°C a 30°C, por ejemplo de -15°C a 0°C, o, por ejemplo, con disiamil-borano ó $LiAlH[OC(CH_3]_3$ en

tetrahidro-furano o dietil-éter, borohidruro de sodio en etanol, o borohidruro de sodio en la presencia de LiCl en diglicol, o similares, a temperaturas preferidas en el intervalo de 0°C hasta la temperatura de reflujo de la mezcla de reacción.

La remoción subsecuente de un grupo protector, por ejemplo PG, tal como terbutoxi-carbonilo, metoxi-metilo, bencilo, 2-(trimetil-silil)-etoxi-carbonilo, o terbutil-dimetil-sililo, si se requiere, tiene lugar bajo condiciones convencionales, ver también la literatura mencionada más adelante bajo las Condiciones Generales del Proceso. Por ejemplo, el terbutoxi-carbonilo se retira en la presencia de un ácido, por ejemplo un ácido halohídrico, tal como HCl, en un solvente apropiado, por ejemplo un éter, tal como dioxano, o un alcohol, por ejemplo isopropanol, a las temperaturas acostumbradas, por ejemplo a temperatura ambiente, la remoción de bencilo mediante el tratamiento con hidrógeno en la presencia de un catalizador de metal noble, tal como paladio sobre carbón, bajo las condiciones de reacción acostumbradas, por ejemplo en un solvente apropiado, tal como metanol o etanol, y a las temperaturas acostumbradas, por ejemplo de 0°C a 50°C, y se puede lograr la remoción de 2-(trimetil-silil)-etoxi-carbonilo, por ejemplo, mediante la reacción con un fluoruro de tetra-alquilo inferior-amonio, tal como fluoruro de tetra-etil-amonio, en un solvente o mezcla de solventes apropiados, por ejemplo un hidrocarburo halogenado, tal como cloruro de metileno, y/o un nitrilo, tal como acetonitrilo, de preferencia a temperaturas

elevadas, por ejemplo bajo condiciones de reflujo, y la remoción del terbutil-dimetil-sililo en la presencia de fluoruro de tetra-butil-amonio, por ejemplo en la presencia de un solvente, tal como tetrahidrofurano, a las temperaturas preferidas de 0°C a 50°C, por ejemplo aproximadamente a la temperatura ambiente.

La reacción adicional según (A) (i) (de preferencia con un compuesto todavía protegido de la Fórmula III) con un compuesto de la Fórmula IV, entonces tiene de preferencia lugar bajo las condiciones acostumbradas para la reacción de sustitución, por ejemplo en un solvente apropiado, tal como un éter, por ejemplo tetrahidrofurano, o un hidrocarburo halogenado, por ejemplo cloruro de metileno, a las temperaturas apropiadas, por ejemplo en el intervalo de -40°C hasta la temperatura de reflujo, si es útil o se requiere, en la presencia de una base, tal como carbonato de potasio. El grupo saliente X es de preferencia halógeno, en especial cloro, bromo o yodo, alcansulfoniloxilo, tal como metansulfoniloxilo, o arilsulfoniloxilo, tal como p-toluol-sulfoniloxilo.

La reacción adicional según (A) (ii) (de preferencia con un compuesto todavía protegido de la Fórmula III) con un compuesto de la Fórmula IV*, alternativamente, entonces de preferencia tiene lugar bajo las condiciones acostumbradas para la reacción de compuestos de hidroxi con isocianatos, por ejemplo, la reacción de preferencia tiene lugar en la presencia de un ácido de Lewis, tal como cloruro de aluminio, en un solvente apropiado, tal como

dietiléter, a temperaturas preferidas, por ejemplo, de 0°C a 50°C. Cuando se requiera, la remoción subsecuente de los grupos protectores tiene lugar como se describe anteriormente o más adelante, en especial como se describe bajo las Condiciones Generales del Proceso.

La aminación reductiva según (B) de preferencia tiene lugar bajo las condiciones acostumbradas para la aminación reductiva, por ejemplo en la presencia de un agente de reducción apropiado (por ejemplo hidrogenación), tal como hidrógeno, en la presencia de un catalizador o de un hidruro complejo, por ejemplo triacetoxi-borohidruro de sodio o ciano-borohidruro de sodio, en un solvente apropiado, tal como un hidrocarburo halogenado, por ejemplo cloruro de metileno ó 1,2-dicloro-etano, y opcionalmente un ácido carbónico, por ejemplo ácido acético, a las temperaturas preferidas de entre -10°C y 50°C, por ejemplo desde 0°C hasta la temperatura ambiente; si se requiere, la remoción subsecuente de los grupos protectores tiene lugar, por ejemplo, como se describe anteriormente en (A).

La condensación de un ácido de la Fórmula II, o un derivado reactivo del mismo, según (C), de preferencia tiene lugar bajo las condiciones de condensación acostumbradas, en donde, entre los posibles derivados reactivos de un ácido de la Fórmula II, se prefieren los ésteres reactivos (tales como los ésteres de hidroxi-benzotriazol (HOBT), pentafluoro-fenilo, 4-nitro-fenilo, o N-hidroxi-succinimida), los haluros de ácido (tales como el cloruro o bromuro

de ácido), o los anhídridos reactivos (tales como los anhídridos mixtos con ácidos alcanoicos inferiores o anhídridos simétricos). Los derivados de ácido carbónico reactivos también, y de preferencia, se pueden formar *in situ*. La reacción se lleva a cabo mediante la disolución de los compuestos de las fórmulas II y VI en un solvente adecuado, por ejemplo un hidrocarburo halogenado, tal como cloruro de metileno, N,N-dimetil-formamida, N,N-dimetil-acetamida, N-metil-2-pirrolidona, cloruro de metileno, o una mezcla de dos o más de estos solventes, y mediante la adición de una base adecuada, por ejemplo trietil-amina, di-isopropil-etil-amina (DIEA), o N-metil-morfolina, y, si se forma *in situ* el derivado reactivo del ácido de la Fórmula II, un agente de acoplamiento adecuado que forme un derivado reactivo preferido del ácido carbónico de la Fórmula III *in situ*, por ejemplo diciclo-hexil-carbodi-imida/1-hidroxi-benzotriazol (DCC/HOBT); cloruro bis-(2-oxo-3-oxazolidinil)-fosfínico (BOPCL); tetrafluoroborato de O-(1,2-dihidro-2-oxo-1-piridil)-N,N,N',N'-tetrametil-uronio (TPTU); tetrafluoroborato de O-(benzotriazol-1-il)-N,N,N',N'-tetrametil-uronio (TBTU); hexa-fluorofosfato de (benzotriazol-1-isoxi)-tri-pirrolidino-fosfonio (PyBOP); clorhidrato de 1-(3-dimetil-amino-propil)-3-etil-carbodi-imida/hidroxi-benzotriazol ó 1-hidroxi-7-aza-benzo-triazol (EDC/HOBT ó EDC/HOAt), ó HOAt solo, o con (1-cloro-2-metil-propenil)-dimetil-amina. Para la revisión de algunos otros posibles agentes de acoplamiento, ver, por ejemplo, Klauser; Bodansky, *Synthesis* 1972, 453-463. La mezcla de reacción de

preferencia se agita a una temperatura de entre aproximadamente -20°C y 50°C, en especial de entre 0°C y 30°C, por ejemplo a temperatura ambiente. La reacción de preferencia se puede llevar a cabo bajo un gas inerte, por ejemplo nitrógeno o argón. Si se requiere, la remoción subsecuente de los grupos protectores tiene lugar, por ejemplo, como se describe anteriormente en (A).

La esterificación según (D) se puede llevar a cabo bajo condiciones de reacción comparables, como se describen para la condensación según (C) descrita en el párrafo anterior, y también los derivados reactivos del ácido de la Fórmula II pueden ser como se describen ahí, si en el compuesto de la Fórmula VII, X es hidroxi. Cuando X es un grupo saliente, en especial halógeno, la reacción tiene lugar en la presencia de una base. Si se requiere, la remoción subsecuente de los grupos protectores tiene lugar, por ejemplo, como se describe anteriormente en (A).

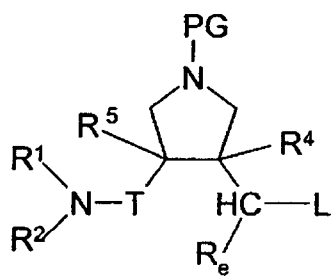
La condensación según la reacción (E)(i) de preferencia tiene lugar bajo las condiciones mencionadas anteriormente para la reacción (C); la esterificación según la reacción (E)(ii) con los compuestos de la Fórmula VII, en donde X es OH, de preferencia tiene lugar bajo las condiciones mencionadas anteriormente para la reacción (D); la reacción (E)(ii) con los compuestos de la Fórmula VII, en donde X es un grupo saliente, de preferencia halógeno, puede tener lugar en la presencia de una base.

Reacciones y Conversiones Opcionales

Los compuestos de la Fórmula I, o las formas protegidas de

los mismos obtenidas directamente de acuerdo con cualquiera de los procedimientos anteriores (significando que, si se desea una conversión, no se requiere una remoción de los grupos protectores de acuerdo con (A), (B), (C), (D), ó (E), o después de introducir grupos protectores nuevos, los cuales se incluyan subsecuentemente como materiales de partida para las conversiones también, incluso cuando no se mencionen de una manera específica, se pueden convertir en compuestos diferentes de la Fórmula I, de acuerdo con los procedimientos conocidos, y cuando se requiera, después de remover los grupos protectores.

Por ejemplo, un compuesto de la Fórmula I, en donde R^1, R^2, R^4, R^5, y T son como se definen para un compuesto de la Fórmula I anteriormente o más adelante, y en donde R^3 es un grupo de la Fórmula (a) mencionada anteriormente, en donde R_e es como se define para un compuesto de la Fórmula I, y R_a es hidrógeno (cuyo compuesto se puede utilizar en forma libre o de preferencia en forma protegida, por ejemplo un compuesto de la Fórmula III dada anteriormente), se puede convertir en el compuesto correspondiente de la Fórmula VIII:



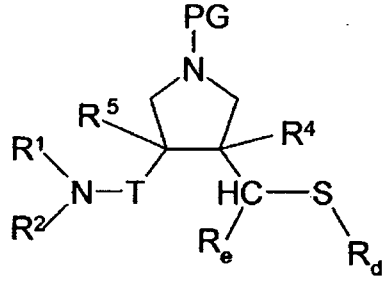
(VIII)

en donde R_e, R^1, R^2, R^4, R^5, y T son como justamente se

definieron, PG es un grupo protector, y L es un grupo saliente, en especial un alcano de 1 a 7 átomos de carbono-sulfoniloxilo, tal como metan-sulfoniloxilo, o aril-sulfoniloxilo, tal como toluen-sulfoniloxilo, de preferencia mediante la reacción con el haluro (por ejemplo cloruro) de alcano o de aril-sulfonilo correspondiente, bajo las condiciones acostumbradas, por ejemplo en ausencia o en la presencia de un solvente apropiado, tal como un éter o un hidrocarburo halogenado, en la presencia de una base de nitrógeno terciaria, tal como trietil-amina, a temperaturas, por ejemplo, de -20°C hasta la temperatura de reflujo de la mezcla de reacción, dando un compuesto correspondiente de la Fórmula VIII; y éste último se puede entonces desproteger para dar el compuesto correspondiente de la Fórmula I, o se puede hacer reaccionar con un compuesto de mercapto de la Fórmula X:

$$R_d\text{-}SH \qquad (X)$$

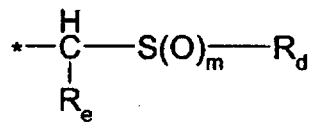
en donde R_d es una fracción como se define para un compuesto de la Fórmula I diferente de aquél de la Fórmula -$N(R_a)(R_b)$, para dar un compuesto correspondiente de la Fórmula XI:



(XI)

en donde R^1, R^2, R^4, R^5, y T son como justamente se

definieron, y PG es un grupo protector, el cual entonces se puede desproteger para dar un compuesto de la Fórmula I, en donde R^3 es una fracción de la Fórmula (c):

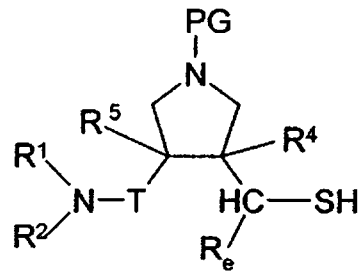


(c)

en donde R_e es como se define para un compuesto de la Fórmula I, **m** es 0 (cero), y R_d es como se define para un compuesto de la Fórmula X; o se puede convertir mediante oxidación, por ejemplo con un peróxido orgánico, tal como ácido m-cloro-perbenzoico, en un solvente apropiado, por ejemplo dimetil-formamida, tetrahidrofurano, o cloruro de metileno, hasta el compuesto correspondiente en donde **m** es 2 que, después de la desprotección, da el compuesto correspondiente de la Fórmula I.

De una manera alternativa, un compuesto de la Fórmula I, en donde R^1, R^2, R^4, R^5, y T son como se definen para los compuestos de la Fórmula I anteriormente o más adelante, y en donde R^3 es un grupo de la Fórmula (a) mencionado anteriormente, en donde R_e es como se define para un compuesto de la Fórmula I, y R_a es hidrógeno (cuyo compuesto se puede utilizar en forma libre o, de preferencia, en forma protegida, por ejemplo, un compuesto de la Fórmula III dado anteriormente), se puede convertir en un compuesto de la Fórmula VIII como se describe anteriormente, el cual entonces se hace reaccionar con un tiolato de alcanoílo de 1 a 7 átomos de carbono, por ejemplo un tiolato de metal alcalino

(tal como sodio), hasta el compuesto correspondiente de la Fórmula XI dado anteriormente, en donde R_d es alcanoílo de 1 a 7 átomos de carbono, tal como acetilo, el cual luego se hidroliza, por ejemplo con hidróxido de litio, bajo las condiciones acostumbradas, para obtener el compuesto de mercapto libre correspondiente de la Fórmula XIA:



(XIA)

el cual entonces:

(i) se hace reaccionar con un compuesto de la Fórmula XA:

$$R_d\text{-Hal} \qquad \text{(XA)}$$

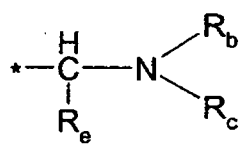
en donde Hal es halógeno, y R_d tiene un significado como se define en la presente diferente de $-N(R_b)(R_c)$, hasta una versión protegida correspondiente de un compuesto de la Fórmula I, que entonces se puede desproteger para dar el compuesto correspondiente de la Fórmula I, en donde R_d es como se define para un compuesto de la Fórmula XA, o el cual se puede oxidar primero para obtener una versión protegida de un compuesto de la Fórmula I, en donde **m** es 1 o de preferencia 2, por ejemplo con un peróxido, tal como ácido m-cloro-perbenzoico, y luego se desprotege para dar el compuesto correspondiente de la Fórmula I; o

(ii) se oxida con un peróxido, tal como peróxido de hidrógeno, y subsecuentemente se hace reaccionar con un agente de halogenación, tal como oxicloruro de fósforo o cloruro de oxalilo, para obtener el compuesto correspondiente en donde, en lugar del grupo SH, está presente un grupo $S(O)_2$-Hal, por ejemplo en donde Hal es halógeno, en especial cloro, el cual entonces se puede hacer reaccionar con un compuesto de la Fórmula VI:

$$R_b\text{-}NH\text{-}R_c \qquad \textbf{(VI)}$$

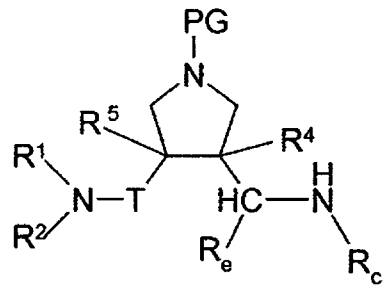
como se define anteriormente, para dar, después de la desprotección, un compuesto correspondiente de la Fórmula I, en donde R_d es un grupo de la Fórmula $-N(R_b)(R_c)$.

Un compuesto de la Fórmula I, en donde R^3 es una fracción de la Fórmula (b):



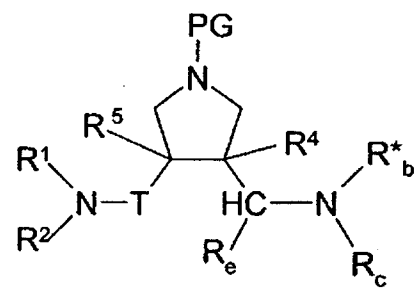
(b)

en donde R_e es como se define para un compuesto de la Fórmula I, R_c es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido, y R_b es hidrógeno, o de preferencia un derivado protegido del mismo, por ejemplo de la Fórmula XII:



(XII)

en donde PG es un grupo protector, y las otras fracciones son como se definen para un compuesto de la Fórmula I, se puede convertir en el compuesto acilado de la Fórmula XIII:



(XIII)

en donde R^*_b es acilo, y las otras fracciones son como se definen para un compuesto de la Fórmula XII, mediante la reacción con un ácido correspondiente de la Fórmula XIV:

$$R^*_b\text{-}OH \qquad \text{(XIV)}$$

en donde R^*_b es acilo, o un derivado reactivo del mismo. La remoción de los grupos protectores conduce entonces al compuesto correspondiente de la Fórmula I, en donde R^3 es una fracción de la Fórmula (b) como justamente se dio, en donde R_e y R_c son como se definen para un compuesto de la Fórmula XII, y R_b es acilo.

Un grupo oxo en un compuesto de la Fórmula I, por ejemplo carbonilo como T, se puede convertir en el grupo tioxo

correspondiente, por ejemplo tiocarbonilo, mediante su reacción con un reactivo de Lawesson bajo las condiciones de reacción acostumbradas.

Las sales de los compuestos de la Fórmula I que tienen cuando menos un grupo formador de sal, se pueden preparar de una manera conocida por sí misma. Por ejemplo, las sales de los compuestos de la Fórmula I que tienen grupos ácido, se pueden formar, por ejemplo, mediante el tratamiento de los compuestos con compuestos de metales, tales como sales de metales alcalinos de ácidos carboxílicos orgánicos adecuados, por ejemplo la sal sódica del ácido 2-etil-hexanoico, con compuestos de metales alcalinos o de metales alcalinotérreos orgánicos, tales como los hidróxidos, carbonatos, o carbonatos ácidos correspondientes, tales como hidróxido, carbonato o carbonato ácido de sodio o de potasio, con los compuestos de calcio correspondientes, o con amoníaco o una amina orgánica adecuada, utilizándose de preferencia cantidades estequiométricas o solamente un pequeño exceso del agente formador de sal. Las sales de adición de ácido de los compuestos de la Fórmula I se obtienen de la manera acostumbrada, por ejemplo, mediante el tratamiento de los compuestos con un ácido o con un reactivo de intercambio de aniones adecuado. Las sales internas de los compuestos de la Fórmula I, que contengan grupos formadores de sales ácidos y básicos, por ejemplo un grupo carboxilo libre y un grupo amino libre, se pueden formar, por ejemplo, mediante la neutralización de

las sales, tales como las sales de adición de ácido, hasta el punto isoeléctrico, por ejemplo con bases débiles, o mediante su tratamiento con intercambiadores de iones.

Una sal de un compuesto de fórmula I puede convertirse de la manera acostumbrada en un compuesto libre; metal y sales de amonio pueden convertirse, por ejemplo, por el tratamiento con ácidos adecuados, y las sales de adición de ácido, por ejemplo, por el tratamiento con un agente básico apropiado. En ambos casos, pueden usarse intercambiadores de iones convenientes.

Las mezclas estereoisoméricas, por ejemplo las mezclas de diaestereómeros, se pueden separar en sus isómeros correspondientes de una manera conocida por sí misma, por medio de métodos de separación apropiados. Las mezclas diaestereoméricas, por ejemplo, se pueden separar en sus diaestereómeros individuales por medio de cristalización fraccionaria, cromatografía, distribución con solvente, y procedimientos similares. Esta separación puede tener lugar ya sea al nivel de uno de los compuestos de partida, o bien en un compuesto de la Fórmula I mismo. Los enantiómeros se pueden separar a través de la formación de sales diaestereoméricas, por ejemplo mediante la formación de sales con un ácido quiral puro en enantiómeros, o por medio de cromatografía, por ejemplo mediante HPLC, utilizando sustratos cromatográficos con ligandos quirales.

Los intermediarios y los productos finales se pueden

procesar y/o purificar de acuerdo con los métodos convencionales, por ejemplo empleando métodos cromatográficos, métodos de distribución, (re-) cristalización, y similares. Algunos posibles métodos que también se pueden emplear con otros compuestos de una manera análoga, se pueden encontrar en los Ejemplos.

Materiales de Inicio

En la siguiente descripción de los materiales de inicio (cuyo término también incluye a los intermediarios) y su síntesis, R^1, R^2, R^3, R^4, R^5, T, m, R_a, R_b, R_c, R_d, R_e, R_f, y PG, tienen los significados dados anteriormente o en los Ejemplos, para los materiales de inicio o intermediarios respectivos, si no se indica de otra manera directamente o por el contexto. Los grupos protectores, si no se mencionan específicamente, se pueden introducir y remover en los pasos apropiados con el objeto de impedir que los grupos funcionales, cuya reacción no se desee en el paso o en los pasos de reacción correspondientes, participen en la reacción, empleando grupos protectores, y los métodos para su introducción y su remoción son como se describen anteriormente o más adelante, por ejemplo en las referencias mencionadas bajo "Condiciones Generales del Proceso". La persona experta en la materia será capaz de decidir fácil-mente si y cuáles grupos protectores son útiles o requeridos, y en cuál etapa es apropiado introducir, intercambiar, y/o remover grupos protectores.

Un compuesto de la Fórmula II, en donde R^*_e es hidrógeno (el cual es un compuesto de la Fórmula V, en donde R^*_e es

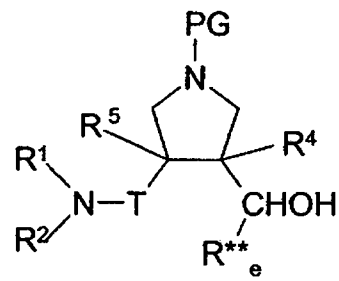
hidrógeno), se puede obtener a partir de un compuesto de la Fórmula IIB o de la Fórmula XV dada más adelante, mediante la reducción de (en el caso de la Fórmula XV esterificada, por ejemplo por alquiloxilo de 1 a 7 átomos de carbono) la función de carboxilo, por ejemplo con un hidruro complejo apropiado, tal como un complejo de borano-sulfuro de dimetilo, en un solvente apropiado, tal como un éter, por ejemplo tetrahidrofurano, a temperaturas preferidas de entre -50°C y la temperatura de reflujo de la mezcla de reacción, por ejemplo de -30°C a 60°C.

Un compuesto de la Fórmula II, en donde R^*_e es arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, o (especialmente) alquilo de 1 a 7 átomos de carbono sustituido, o de preferencia insustituido (el cual es un compuesto de la Fórmula V en donde R_e es arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, o (especialmente) alquilo de 1 a 7 átomos de carbono sustituido, o de preferencia insustituido), por ejemplo, se puede obtener a partir de un compuesto de la Fórmula V, en donde R^*_e es hidrógeno, mediante la reacción con un reactivo de Grignard de la Fórmula XXII:

R^{**}_e-Mg-Hal **(XXII)**

en donde R^{**}_e es arilo mono- o bi-cíclico-alquilo insustituido

o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, o (especialmente) alquilo de 1 a 7 átomos de carbono sustituido, o de preferencia insustituido, y Hal es halógeno, en especial cloro o bromo, bajo las condiciones de reacción acostumbradas, por ejemplo en un éter, tal como dietil-éter, a las temperaturas preferidas desde 0°C hasta la temperatura de reflujo de la mezcla de reacción, para dar un compuesto de la Fórmula IIIA:



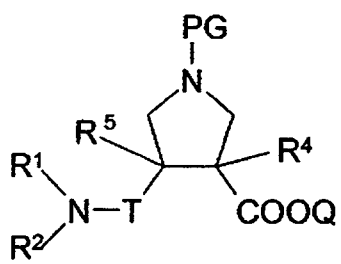
(IIIA)

en donde R^{**}_e es como justamente se describió (el cual es un compuesto de la Fórmula III, en donde R^*_e es como justamente se definió para R^{**}_e); el cual entonces se oxida, por ejemplo en la presencia de un oxidante apropiado, tal como peryodinano de Dess-Martin, en un solvente apropiado, por ejemplo un hidrocarburo halogenado, por ejemplo cloruro de metileno, a las temperaturas preferidas de 0°C a 50°C, por ejemplo a temperatura ambiente, para dar el compuesto correspondiente de la Fórmula II ó V.

De una manera alternativa, un compuesto de la Fórmula II, en donde R^*_e es arilo mono- o bi-cíclico-alquilo insustituido o

sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, o (especialmente) alquilo de 1 a 7 átomos de carbono sustituido, o de preferencia insustituido, se puede hacer reaccionar en la presencia de un agente de condensación, por ejemplo bajo condiciones de reacción y con reactivos como se describen bajo las variantes del proceso (C) y (D) anteriores, con N,O-dimetil-hidroxil-amina, para formar la amida de Weinreb correspondiente, la cual entonces se puede hacer reaccionar directamente con un reactivo de Grignard de la Fórmula XXII, como se describe anteriormente, para obtener un compuesto correspondiente de la Fórmula II ó V.

Un compuesto de la Fórmula IIB (el cual es un compuesto de la Fórmula II en donde R^*_e es hidroxi), se puede preparar a partir de un éster correspondiente de la Fórmula XV:

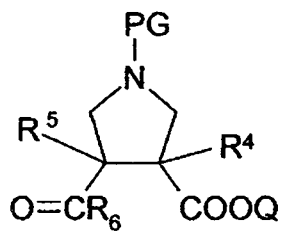


(XV)

en donde Q es una fracción orgánica, de preferencia alquilo de 1 a 7 átomos de carbono sustituido, o en especial insustituido, mediante hidrólisis en la presencia de una base, por ejemplo un hidróxido de metal alcalino, tal como hidróxido de litio, en un solvente apropiado, por ejemplo un hidroxi-alcano inferior, tal

como metanol, en la presencia de agua, y de preferencia a temperaturas, por ejemplo, de 0°C a 50°C.

Un compuesto de la Fórmula XV en donde T es metileno, o metileno mono-sustituido por alquilo (-[C(H) (alquilo)]-), por ejemplo, se puede obtener mediante la reacción de un compuesto de aldehído o queto de la Fórmula XVI:



(XVI)

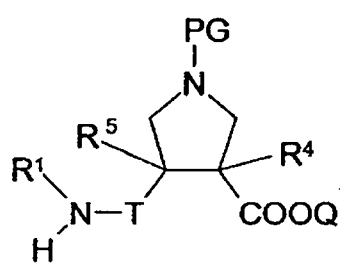
en donde Q es como se describe para un compuesto de la Fórmula XV, y R_6 es alquilo, o de preferencia hidrógeno, con una amina de la Fórmula XVII:

$$R^1\text{-}NH\text{-}R^2 \qquad \textbf{(XVII)}$$

bajo condiciones de aminación reductiva, por ejemplo bajo las condiciones de reacción descritas para la reacción (B) anterior. Si en lugar de un compuesto de la Fórmula XVII, se utiliza un compuesto de la Fórmula XVII*:

$$H_2\text{-}N\text{-}R_1 \qquad \textbf{(XVII*)}$$

resulta un compuesto de la Fórmula XV*:



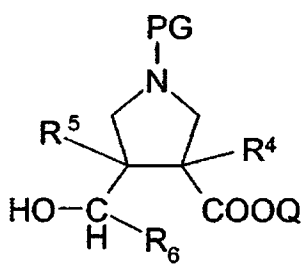
(XV*)

en donde Q es como se define para un compuesto de la Fórmula XV, el cual entonces se puede convertir en un compuesto de la Fórmula XV mediante su reacción con un compuesto de la Fórmula XVIII:

$$R_2\text{-}Y \qquad \textbf{(XVIII)}$$

en donde Y, si R_2 es acilo, es hidroxi o bien el compuesto es un derivado reactivo, por ejemplo, en donde Y es halógeno o un grupo activador formado *in situ*, de preferencia bajo condiciones análogas a las de la reacción (C) anterior; o Y, si R_2 es una de las fracciones definidas para R_2 en los compuestos de la Fórmula I diferente de acilo, es un grupo saliente, por ejemplo como se define para X en un compuesto de la Fórmula IV anterior, y bajo condiciones de reacción análogas a las descritas anteriormente para la reacción según (A)(i).

Un compuesto de la Fórmula XVI, en donde R_6 es alquilo, o de preferencia hidrógeno, por ejemplo, se puede obtener a partir de un compuesto de hidroxi de la Fórmula XIX:

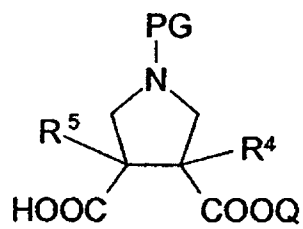


(XIX)

en donde R_6 es alquilo o de preferencia hidrógeno, y Q es como se define para un compuesto de la Fórmula XV, mediante oxidación hasta el compuesto oxo correspondiente de la Fórmula

XVI, que tiene lugar de preferencia en la presencia de un oxidante apropiado, tal como peryodinano de Dess-Martin, en un solvente apropiado, por ejemplo un hidrocarburo halogenado, por ejemplo cloruro de metileno, a las temperaturas preferidas de 0°C a 50°C, por ejemplo a temperatura ambiente.

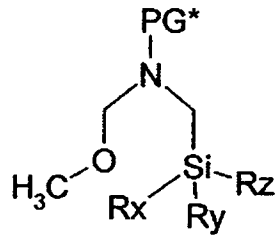
Un compuesto de hidroxi de la Fórmula XIX, en donde R_6 es hidrógeno, por ejemplo, se puede obtener a partir de un compuesto de la Fórmula XX:



(XX)

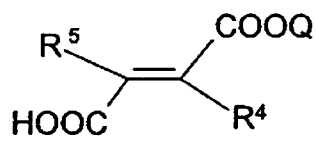
en donde Q es como se define para un compuesto de la Fórmula XV, mediante reducción en la presencia de un hidruro complejo apropiado, por ejemplo un complejo de borano-sulfuro de dimetilo, en un solvente apropiado, tal como un éter, por ejemplo tetrahidrofurano, a las temperaturas preferidas entre -50°C y la temperatura de reflujo de la mezcla de reacción, por ejemplo, de -30°C a 60°C.

Un compuesto de la Fórmula XX, entre otras cosas, se puede obtener mediante la reacción de un compuesto de la Fórmula XXI:



(XXI)

en donde PG* es un grupo protector que soporta la reacción, por ejemplo bencilo, y cada uno de Rx, Ry, y Rz son alquilo, de preferencia alquilo de 1 a 7 átomos de carbono, en especial metilo, con un derivado de ácido fumárico de la Fórmula XXII:

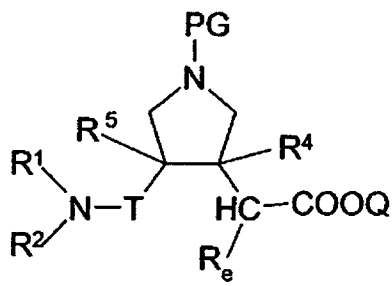


(XXII)

en donde cada uno de R^4 y R^5 tiene de preferencia uno de los significados dados para R^4 y R^5 diferente de hidroxi, más preferiblemente es alquilo de 1 a 7 átomos de carbono, por ejemplo metilo o etilo, o es hidrógeno, en la presencia de un ácido, por ejemplo ácido trifluoroacético, en un solvente apropiado, tal como un hidrocarburo halogenado, por ejemplo cloruro de metileno, a las temperaturas preferidas, por ejemplo, en el intervalo de -30°C a 50°C, produciendo el compuesto correspondiente de la Fórmula XX, en donde de preferencia el grupo protector PG* puede ser reemplazado con un grupo protector PG diferente útil para las siguientes reacciones, tal como terbutoxi-carbonilo, por ejemplo bencilo; el PG* se puede remover con hidrógeno en la presencia de un catalizador de hidrogenación,

en especial un catalizador de metal noble, de preferencia sobre un material portador, tal como carbón, por ejemplo Pd/C, en un solvente apropiado, tal como un alcohol, por ejemplo etanol, a temperaturas, por ejemplo, de -10°C a 60°C, y se puede introducir el terbutoxi-carbonilo en el mismo paso o subsecuentemente mediante la reacción con anhídrido terbutoxi-carbónico.

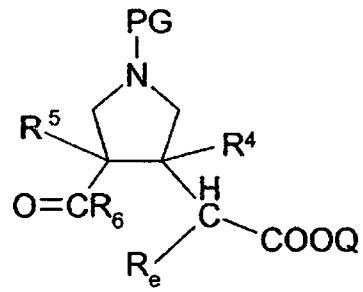
Un compuesto de la Fórmula IIA, por ejemplo, se puede preparar a partir de un éster correspondiente de la Fórmula XVA:



(XVA)

en donde Q es una fracción orgánica, de preferencia alquilo de 1 a 7 átomos de carbono sustituido, en especial insustituido, mediante hidrólisis en la presencia de una base, por ejemplo un hidróxido de metal alcalino, tal como hidróxido de litio, en un solvente apropiado, por ejemplo un hidroxi-alcano inferior, tal como metanol, en la presencia de agua, y de preferencia a temperaturas, por ejemplo, de 0°C a 50°C.

Un compuesto de la Fórmula XVA, en donde T es metileno, o metileno mono-sustituido por alquilo (-[C(H) (alquilo)]-), por ejemplo, se puede obtener mediante la reacción de un compuesto de aldehído o queto de la Fórmula XVIA:



(XVIA)

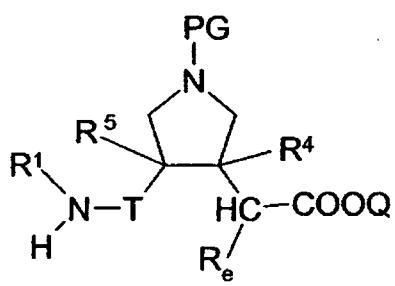
en donde Q es como se describe para un compuesto de la Fórmula XVA, y R_6 es alquilo o de preferencia hidrógeno, con una amina de la Fórmula XVII:

$$R^1\text{-}NH\text{-}R^2 \qquad \text{(XVII)}$$

bajo condiciones de aminación reductiva, por ejemplo bajo las condiciones de reacción descritas para la reacción (B) anterior. Si, en lugar de un compuesto de la Fórmula XVII, se utiliza un compuesto de la Fórmula XVII*:

$$H_2\text{-}N\text{-}R_1 \qquad \text{(XVII*)}$$

resulta un compuesto de la Fórmula XVA*:



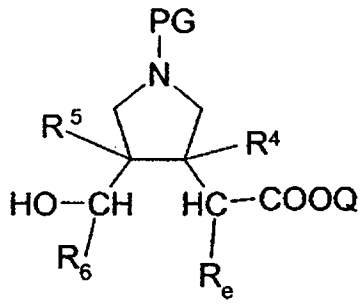
(XVA*)

en donde Q es como se define para un compuesto de la Fórmula XVA, el cual entonces se puede convertir en un compuesto de la Fórmula XVA, mediante su reacción con un compuesto de la Fórmula XVIII:

$$R_2\text{-}Y \qquad \text{(XVIII)}$$

en donde Y, si R_2 es acilo, es hidroxi o el compuesto es un derivado reactivo, por ejemplo en donde Y es halógeno o un grupo activador formado *in situ*, de preferencia bajo condiciones análogas a aquéllas de la reacción (C) anterior; o Y, si R_2 es una de las fracciones definidas para R_2 en los compuestos de la Fórmula I diferente de acilo, es un grupo saliente, por ejemplo como se define para X en un compuesto de la Fórmula IV anterior, o bajo condiciones de reacción análogas a las descritas anteriormente para la reacción según (A)(i).

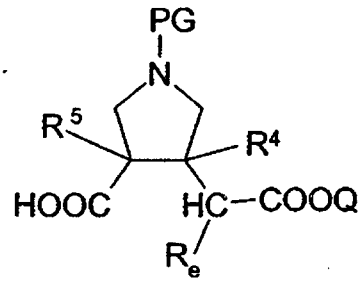
Un compuesto de la Fórmula XVIA, en donde R_6 es alquilo o de preferencia hidrógeno, por ejemplo, se puede obtener a partir de un compuesto de hidroxi de la Fórmula XIXA:



(XIXA)

en donde R_6 es alquilo o de preferencia hidrógeno, y Q es como se define para un compuesto de la Fórmula XVA, mediante oxidación hasta el compuesto oxo correspondiente de la Fórmula XVIA, que de preferencia tiene lugar en la presencia de un oxidante apropiado, tal como peryodinano de Dess-Martin, en un solvente apropiado, por ejemplo un hidrocarburo halogenado, por ejemplo cloruro de metileno, a las temperaturas preferidas de 0°C a 50°C, por ejemplo a temperatura ambiente.

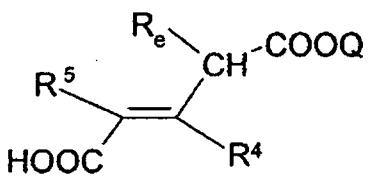
Un compuesto de hidroxi de la Fórmula XIXA, en donde R_6 es hidrógeno, por ejemplo, se puede obtener a partir de un compuesto de la Fórmula XXA:



(XXA)

en donde Q es como se define para un compuesto de la Fórmula XV, mediante reducción en la presencia de un hidruro complejo apropiado, por ejemplo un complejo de borano-sulfuro de dimetilo, en un solvente apropiado, tal como un éter, por ejemplo tetrahidrofurano, a las temperaturas preferidas de entre -50°C y la temperatura de reflujo de la mezcla de reacción, por ejemplo de -30°C a 60°C.

Un compuesto de la Fórmula XXA se puede obtener, entre otras cosas, mediante la reacción de un compuesto de la Fórmula XXI, como se describe anteriormente, con un derivado de ácido fumárico de la Fórmula XXIA:



(XXIA)

en donde cada uno de R^4 y R^5 de preferencia tiene uno de los significados dados para R^4 y R^5 diferente de hidroxi, más

preferiblemente es alquilo de 1 a 7 átomos de carbono, por ejemplo metilo o etilo, o es hidrógeno, en la presencia de un ácido, por ejemplo ácido trifluoroacético, en un solvente apropiado, tal como un hidrocarburo halogenado, por ejemplo cloruro de metileno, a las temperaturas preferidas, por ejemplo, en el intervalo de -30°C a 50°C, produciendo el compuesto correspondiente de la Fórmula XXA, en donde de preferencia el grupo protector PG* puede ser reemplazado con un grupo protector PG diferente útil para las siguientes reacciones, tal como terbutoxi-carbonilo, por ejemplo bencilo. El PG* se puede remover con hidrógeno en la presencia de un catalizador de hidrogenación, en especial un catalizador de metal noble, de preferencia sobre un material portador, tal como carbón, por ejemplo Pd/C, en un solvente apropiado, tal como un alcohol, por ejemplo etanol, a temperaturas, por ejemplo, de -10°C a 60°C, y se puede introducir el terbutoxi-carbonilo en el mismo paso o subsecuentemente mediante su reacción con anhídrido terbutoxicarbónico.

Un compuesto de la Fórmula IIA también se puede obtener mediante la reacción de un compuesto de la Fórmula VIII como se describe anteriormente, con una sal de cianuro, por ejemplo un cianuro de metal alcalino, tal como cianuro de sodio o de potasio, hasta el compuesto correspondiente, en donde, en lugar del grupo -C(H)(R_e)-L, está presente un grupo -C(H)(R_e)-CN, seguido por la hidrólisis con una base, tal como hidróxido de sodio, o bajo condiciones ligeras, mediante la reacción primero con H_2S, dando

como resultado una tioamida correspondiente, la cual entonces se puede hidrolizar bajo condiciones ligeras, para dar un compuesto correspondiente de la Fórmula IIA.

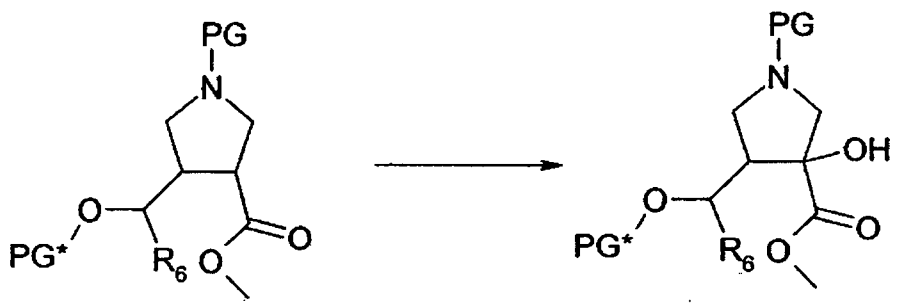
Un compuesto de la Fórmula XV o XVA, en donde T es carbonilo (y Q es como se define para los compuestos de la Fórmula XV anterior), por ejemplo, se puede obtener mediante la reacción de un compuesto de la Fórmula XX ó XXA, respectivamente, como se define anteriormente, o un derivado reactivo del mismo, bajo condiciones análogas a las descritas anteriormente para la reacción de condensación bajo la variante del proceso (C), con un compuesto de la Fórmula XVII como se define anteriormente.

En los materiales de inicio anteriores (y en los productos finales), R^4 y R^5 son de preferencia hidrógeno, con menos preferencia alquilo insustituido o sustituido, hidroxi esterificado o eterificado, y con todavía menos preferencia (en los intermediarios preferiblemente protegidos), hidroxi.

R^4 y/o R^5 como hidroxi, se puede introducir en los materiales de inicio en diferentes etapas, por ejemplo en los compuestos (de preferencia apropiadamente protegidos) de la Fórmula XV, por ejemplo mediante el tratamiento con una base fuerte para remover el hidrógeno que vaya a ser sustituido por R^4 o R^5, tal como hexametil-disilazida de litio (LHMDS), o de preferencia di-isopropil-amida de litio, en tetrahidrofurano, a bajas temperaturas, por ejemplo de -100°C a -50°C, tal como a -78°C,

seguido por oxidación, por ejemplo, mediante la adición de un derivado de oxaziridina de acuerdo con Davis (por ejemplo, 2-terbutoxi-carbonil-3-tricloro-metil-oxaziridina ó 2-(fenil-sulfonil o tolil-sulfonil)-3-fenil-oxaziridina ó (por ejemplo, para la síntesis estereo-selectiva) (+)- ó (-)-(canforsulfonil)-oxaziridina, para dar el compuesto de hidroxi correspondiente.

Una alternativa es la transformación sobre el siguiente alcohol protegido por O mostrado a la izquierda (un compuesto de la Fórmula XIX), para dar un intermediario (mostrado a la derecha, también un compuesto de la Fórmula XIX) que se puede utilizar ya sea para construir una pirrolidina final en donde R^5 ó R^4 son OH o hidroxi eterificado o esterificado, dependiendo de la secuencia de reacciones empleada:



en donde, en ambas fórmulas, PG* es un grupo protector de hidroxi, bajo condiciones de reacción comparables como justamente se mencionó, u otras condiciones acostumbradas.

R^4 y/o R^5 como hidroxi, se puede entonces además esterificar o eterificar de acuerdo con los procedimientos convencionales, para dar los compuestos correspondientes en donde R^4 y/o R^5 es hidroxi esterificado o eterificado.

En la técnica se conocen otros materiales de inicio, tales como también los materiales de inicio de las fórmulas IV, IV*, VI, VII, X, y XIV, y se pueden preparar de acuerdo con los métodos que son conocidos en la materia y/o que están comercialmente disponibles.

Condiciones Generales del Proceso

Lo siguiente se aplica en general a todos los procesos mencionados anteriormente en la presente y más adelante en la presente, mientras que se prefieren las condiciones de reacción específicamente mencionadas anteriormente o más adelante:

En cualquiera de las reacciones mencionadas anteriormente en la presente y más adelante en la presente, se pueden utilizar grupos protectores cuando sea apropiado o se desee, aun cuando esto no se mencione de una manera específica, para proteger a los grupos funcionales que no se pretenda que tomen parte en una reacción dada, y se pueden introducir y/o remover en las etapas apropiadas o deseadas. Por consiguiente, se incluyen como posibles las reacciones que comprendan el uso de grupos protectores, siempre que se describan reacciones sin mencionar específicamente la protección y/o desprotección en esta memoria descriptiva.

Dentro del alcance de esta divulgación, solamente se designa como un "grupo protector" a un grupo fácilmente removible que no sea un constituyente del producto final deseado particular, a menos que el contexto lo indique de otra manera. La protección

de los grupos funcionales mediante estos grupos protectores, los grupos protectores mismos, y las reacciones apropiadas para su introducción y remoción, se describen, por ejemplo, en los trabajos de referencia convencionales, tales como J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, Londres y Nueva York 1973, en T. W. Greene y P. G. M. Wuts, "Protective Groups in Organic Synthesis", Tercera Edición, Wiley, Nueva York 1999, en "The Peptides"; Volumen 3 (Editores: E. Gross y J. Meienhofer), Academic Press, Londres y Nueva York 1981, en "Methoden der organischen Chemie" (*Métodos de Química Orgánica*), Houben Weyl, 4ª Edición, Volumen 15/I, Georg Thieme Verlag, Stuttgart 1974, en H. D. Jakubke y H. Jeschkeit, "Aminosäuren, Peptide, Proteine" (*Amino acids, Peptides, Proteins*), Verlag Chemie, Weinheim, Deerfield Beach, y Basilea 1982, y en Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate" (*Chemistry of Carbohydrates: Monosaccharides and Derivatives*), Georg Thieme Verlag, Stuttgart 1974. Una característica de los grupos protectores es que se pueden remover fácilmente (es decir, sin la presentación de reacciones secundarias indeseadas), por ejemplo mediante solvólisis, reducción, fotólisis, o alternativamente bajo condiciones fisiológicas (por ejemplo, mediante disociación enzimática).

Todos los pasos de proceso anteriormente mencionados se pueden llevar a cabo bajo las condiciones de reacción que son conocidas por sí mismas, de preferencia las mencionadas de una

manera específica, en ausencia, o, por costumbre, en la presencia de solventes o diluyentes, de preferencia solventes o diluyentes que sean inertes hacia los reactivos utilizados y que los disuelvan, en ausencia o en la presencia de catalizadores, agentes de condensación o neutralización, por ejemplo intercambiadores de iones, tales como intercambiadores de cationes, por ejemplo en la forma de H^+, dependiendo de la naturaleza de la reacción y/o de los reactivos, a temperatura reducida, normal, o elevada, por ejemplo en un intervalo de temperatura de aproximadamente -100°C a aproximadamente 190°C, de preferencia de aproximadamente -80°C a aproximadamente 150°C, por ejemplo de -80°C a -60°C, a temperatura ambiente, de -20°C a aproximadamente 40°C, o a la temperatura de reflujo, bajo presión atmosférica o en un recipiente cerrado, donde sea apropiado bajo presión, y/o en una atmósfera inerte, por ejemplo bajo una atmósfera de argón o nitrógeno.

Los solventes a partir de los cuales se pueden seleccionar aquellos solventes que sean adecuados para cualquier reacción particular incluyen los mencionados de una manera específica, o, por ejemplo, agua, ésteres, tales como alcanoatos inferiores de alquilo inferior, por ejemplo acetato de etilo, éteres, tales como éteres alifáticos, por ejemplo dietil-éter, o éteres cíclicos, por ejemplo tetrahidro-furano o dioxano, hidrocarburos aromáticos líquidos, tales como benceno o tolueno, alcoholes, tales como metanol, etanol, o 1- ó 2-propanol, nitrilos, tales como acetonitrilo,

hidrocarburos halogenados, por ejemplo como cloruro de metileno o cloroformo, amidas de ácido, tales como dimetil-formamida o dimetil-acetamida, bases, tales como bases de nitrógeno heterocíclico, por ejemplo piridina o N-metil-pirrolidin-2-ona, anhídridos de ácido carboxílico, tales como anhídridos de ácido alcanoico inferior, por ejemplo anhídrido acético, hidrocarburos cíclicos, lineales o ramificados, tales como ciclo-hexano, hexano, o iso-pentano, o mezclas de los mismos, por ejemplo soluciones acuosas, a menos que se indique de otra manera en la descripción de los procesos. Estas mezclas de solventes también se pueden utilizar en el procesamiento, por ejemplo mediante cromatografía o división.

La invención se refiere también a las formas de los procesos en donde se utiliza un compuesto que se pueda obtener como intermediario en cualquier etapa del proceso como material de inicio, y se llevan a cabo los pasos restantes del proceso, o en donde se forma un material de inicio bajo las condiciones de la reacción, o se utiliza en la forma de un derivado, por ejemplo en una forma protegida o en la forma de una sal, o se produce un compuesto que se pueda obtener mediante el proceso de acuerdo con la invención bajo las condiciones del proceso, y se procesa adicionalmente *in situ*. En los procesos de la presente invención, de preferencia se utilizan los materiales de inicio que den como resultado los compuestos de la Fórmula I descritos como preferidos. Se da una preferencia especial a las condiciones de

reacción que sean idénticas o análogas a las mencionadas en los Ejemplos. La invención también se refiere a los compuestos de inicio e intermediarios novedosos descritos en la presente, en especial a aquéllos que conduzcan a los compuestos novedosos de la Fórmula I, o a los compuestos de la Fórmula I mencionados como preferidos en la presente.

Uso farmacéutico, preparaciones farmacéuticas,y métodos.

Como se describe en lo anterior, los compuestos de la presente invención son inhibidores de la actividad de la renina y, por lo tanto, pueden ser útiles para el tratamiento de hipertensión, ateroesclerosis, síndrome coronario inestable, insuficiencia cardíaca congestiva, hipertrofia cardíaca, fibrosis cardíaca, cardiomiopatía posterior a infarto, síndrome coronario inestable, disfunción diastólica, enfermedad crónica del riñón, fibrosis hepática, complicaciones resultantes de diabetes, tales como nefropatía, vasculopatía y neuropatía, enfermedades de los vasos coronarios, restenosis en seguida de angioplastía, presión intra-ocular elevada, glaucoma, crecimiento vascular anormal y/o hiperaldosteronismo, y/o además, deterioro cognoscitivo, enfermedad de Alzheimer, demencia, estados de ansiedad y trastornos cognoscitivos, y similares. Se prefiere en especial la hipertensión, cuando menos como un componente de la enfermedad que se vaya a tratar, significando que se puede tratar (profilácticamente y/o terapéuticamente) la hipertensión sola o en

combinación con una o más enfermedades adicionales (en especial de las mencionadas).

La presente invención proporciona además composiciones farmacéuticas que comprenden una cantidad terapéuticamente efectiva de un compuesto farmacológica-mente activo de la presente invención, solo o en combinación con uno o más vehículos farmacéuticamente aceptables.

Las composiciones farmacéuticas de acuerdo con la presente invención son aquéllas adecuadas para administración enteral, tal como oral o rectal, transdérmica y parenteral a mamíferos, incluyendo el hombre, con el fin de inhibir la actividad de la renina, y para el tratamiento de condiciones asociadas con la actividad de la renina (especialmente inapropiada). Estas condiciones incluyen hipertensión, ateroesclerosis, síndrome coronario inestable, insuficiencia cardíaca congestiva, hipertrofia cardíaca, fibrosis cardíaca, cardiomiopatía posterior a infarto, síndrome coronario inestable, disfunción diastólica, enfermedad crónica del riñón, fibrosis hepática, complicaciones resultantes de diabetes, tales como nefropatía, vasculopatía y neuropatía, enfermedades de los vasos coronarios, restenosis en seguida de angioplastía, presión intra-ocular elevada, glaucoma, crecimiento vascular anormal, y/o hiperaldosteronismo, y/o además, deterioro cognoscitivo, enfermedad de Alzheimer, demencia, estados de ansiedad y trastornos cognoscitivos, y similares. Se prefiere en especial una enfermedad que comprenda hipertensión, más

especialmente la hipertensión misma, en donde el tratamiento con una composición farmacéutica o el uso de un compuesto de la Fórmula I sea útil profiláctica-mente y/o (de preferencia) terapéuticamente.

Por consiguiente, los compuestos farmacológica-mente activos de la invención se pueden emplear en la fabricación de composiciones farmacéuticas que comprendan una cantidad efectiva de los mismos en conjunto o en mezcla con excipientes o vehículos adecuados para aplicación enteral o parenteral. Se prefieren las tabletas y las cápsulas de gelatina que comprendan al ingrediente activo junto con:

a) diluyentes, por ejemplo lactosa, dextrosa, sacarosa, manitol, sorbitol, celulosa, y/o glicina;

b) lubricantes, por ejemplo sílice, talco, ácido esteárico, su sal de magnesio o calcio, y/o polietilenglicol; para tabletas también,

c) aglutinantes, por ejemplo silicato de magnesio y aluminio, pasta de almidón, gelatina, tragacanto, metil-celulosa, carboxi-metil-celulosa de sodio, y/o polivinil-pirrolidona; si se desea,

d) desintegrantes, por ejemplo almidones, ágar, ácido algínico o su sal sódica, o mezclas efervescentes; y/o

e) absorbentes, colorantes, saborizantes, y edulcorantes.

Las composiciones inyectables de preferencia son soluciones o suspensiones isotónicas acuosas, y los supositorios

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se preparan de una manera conveniente a partir de emulsiones o suspensiones grasas.

Estas composiciones se pueden esterilizar y/o pueden contener adyuvantes, tales como agentes conservadores, estabilizantes, humectantes, o emulsionantes, promotores de solución, sales para regular la presión osmótica, y/o reguladores del pH. En adición, también pueden contener otras sustancias terapéuticamente valiosas. Estas composiciones se preparan de acuerdo con los métodos convencionales de mezcla, granulación, o recubrimiento, respectivamente, y contienen de aproximadamente el 0.1 al 75 por ciento, de preferencia de aproximadamente el 1 al 50 por ciento del ingrediente activo.

Las formulaciones adecuadas para aplicación transdérmica incluyen una cantidad terapéuticamente efectiva de un compuesto de la invención con un vehículo. Los vehículos convenientes incluyen solventes farmacológica-mente aceptables absorbibles para ayudar al paso a través de la piel del huésped. De una manera característica, los dispositivos transdérmicos están en la forma de un parche que comprende un miembro de respaldo, un depósito que contiene al compuesto opcionalmente con vehículos, opcionalmente una barrera de control de velocidad para suministrar el compuesto a la piel del huésped a una velocidad controlada y previamente determinada durante un período de tiempo prolongado, y medios para asegurar el dispositivo a la piel.

De conformidad con lo anterior, la presente invención

proporciona composiciones farmacéuticas como se describen anteriormente para el tratamiento de condiciones mediadas por la actividad de la renina, de preferencia hipertensión, ateroesclerosis, síndrome coronario inestable, insuficiencia cardíaca congestiva, hipertrofia cardíaca, fibrosis cardíaca, cardiomiopatía posterior a infarto, síndrome coronario inestable, disfunción diastólica, enfermedad crónica del riñón, fibrosis hepática, complicaciones resultantes de diabetes, tales como nefropatía, vasculopatía, y neuropatía, enfermedades de los vasos coronarios, restenosis en seguida de angioplastía, presión intraocular elevada, glaucoma, crecimiento vascular anormal, y/o hiperaldosteronismo, y/o además deterioro cognoscitivo, enfermedad de Alzheimer, demencia, estados de ansiedad y trastornos cognoscitivos, así como los métodos para su uso.

Las composiciones farmacéuticas pueden contener una cantidad terapéuticamente efectiva de un compuesto de la Fórmula I como se define en la presente, ya sea solo o en una combinación con otro agente terapéutico, por ejemplo cada uno en una dosis terapéuticamente efectiva como se reporta en la materia. Estos agentes terapéuticos incluyen:

a) agentes antidiabéticos, tales como insulina, derivados de insulina, y miméticos; secretagogos de insulina, tales como las sulfonil-ureas, por ejemplo Glipizida, gliburida, y Amarilo; ligandos del receptor de sulfonil-urea insulinotrópicos, tales como meglitinidas, por ejemplo nateglinida y repaglinida; ligandos del

receptor activado por el proliferador de peroxisoma (PPAR); inhibidores de fosfatasa de proteína tirosina-1B (PTP-1B), tales como PTP-112; inhibidores de GSK3 (quinasa-3 de sintasa de glicógeno), tales como SB-517955, SB-4195052, SB-216763, NN-57-05441, y NN-57-05445; ligandos RXR, tales como GW-0791 y AGN-194204; inhibidores del co-transportador de glucosa dependiente de sodio, tales como T-1095; inhibidores de la fosforilasa A de glicógeno, tales como BAY R3401; biguanidas, tales como met-formina; inhibidores de alfa-glucosidasa, tales como acarbosa; GLP-1 (péptido-1 tipo glucagon), análogos de GLP-1, tales como Exendina-4 y miméticos de GLP-1; e inhibidores de DPPIV (dipeptidil-peptidasa IV), tales como LAF-237;

b) agentes hipolipidémicos, tales como inhibidores de la reductasa de 3-hidroxi-3-metil-glutaril-coenzima A (HMG-CoA), por ejemplo lovastatina, pitavastatina, simvastatina, pravastatina, cerivastatina, mevastatina, velostatina, fluvastatina, dalvastatina, atorvastatina, rosuvastatina, y rivastatina; inhibidores de sintasa de escualeno; ligandos FXR (receptor farnesoide X) y LXR (receptor de hígado X); colestiramina; fibratos; ácido nicotínico, y aspirina;

c) agentes contra la obesidad, tales como orlistato; y

d) agentes anti-hipertensivos, por ejemplo diuréticos de ciclo, tales como ácido etacrínico, furosemida, y torsemida; inhibidores de la enzima convertidora de angiotensina (ACE), tales como benazepril, captopril, enalapril, fosinopril, lisinopril,

moexipril, perinodopril, quinapril, ramipril, y trandolapril; inhibidores de la bomba de membrana Na-K-ATPasa, tales como digoxina; inhibidores de neutralendopeptidasa (NEP); inhibidores de ACE/NEP, tales como omapatrilato, sampatrilato, y fasidotril; antagonistas de angiotensina II, tales como candesartan, eprosartan, irbesartan, losartan, telmisartan, y valsartan, en particular valsartan; bloqueadores del receptor adrenérgico-β, tales como acebutolol, atenolol, betaxolol, bisoprolol, metoprolol, nadolol, propanolol, sotalol y timolol; agentes inotrópicos tales como digoxina, dobutamina, y milrinona; bloqueadores del canal de calcio, tales como amlodipina, bepridil, diltiazem, felodipina, nicardipina, nimodipina, nifedipina, nisoldipina, y verapamil; antagonistas del receptor de aldosterona; e inhibidores de la sintasa de aldosterona.

Otros compuestos anti-diabéticos específicos son descritos por Patel Mona en *Expert Opin. Invest. Drugs*, 2003, 12(4), 623-633, en las Figuras 1 a 7, las cuales se incorporan a la presente como referencia. Un compuesto de la presente invención se puede administrar ya sea de una manera simultánea, antes, o después del otro ingrediente activo, ya sea por separado por la misma vía de administración o por una diferente, o juntos en la misma formulación farmacéutica.

La estructura de los agentes terapéuticos identificados por números de código, nombres genéricos o comerciales, se puede tomar de la edición actual del compendio estándar "The Merck

Index", o de las bases de datos, por ejemplo Patents International (por ejemplo, IMS World Publications). El contenido correspondiente de las mismas se incorpora a la presente como referencia.

De conformidad con lo anterior, la presente invención proporciona productos o composiciones farmacéuticas que comprenden una cantidad terapéuticamente efectiva de un compuesto de la invención, solo o en combinación con una cantidad terapéuticamente efectiva de otro agente terapéutico, de preferencia seleccionado a partir de anti-diabéticos, agentes hipolipidémicos, agentes contra la obesidad, o agentes anti-hipertensivos, más preferiblemente a partir de anti-diabéticos, agentes anti-hipertensivos, o agentes hipolipidémicos, como se describen anteriormente.

La presente invención se refiere además a composiciones farmacéuticas como se describen en lo anterior, para utilizarse como un medicamento.

La presente invención se refiere además al uso de composiciones farmacéuticas o combinaciones como se describen anteriormente para la preparación de un medicamento para el tratamiento de condiciones mediadas por una actividad (especialmente inapropiada) de la renina, de preferencia hipertensión, ateroesclerosis, síndrome coronario inestable, insuficiencia cardíaca congestiva, hipertrofia cardíaca, fibrosis cardíaca, cardiomiopatía posterior a infarto, síndrome coronario

inestable, disfunción diastólica, enfermedad crónica del riñón, fibrosis hepática, complicaciones resultantes de diabetes, tales como nefropatía, vasculopatía, y neuropatía, enfermedades de los vasos coronarios, restenosis en seguida de angioplastía, presión intraocular elevada, glaucoma, crecimiento vascular anormal, y/o hiperaldosteronismo, y/o además, deterioro cognoscitivo, enfermedad de Alzheimer, demencia, estados de ansiedad, y trastornos cognoscitivos, y similares.

Por consiguiente, la presente invención también se refiere a un compuesto de la Fórmula I para utilizarse como un medicamento, al uso de un compuesto de la Fórmula I para la preparación de una composición farmacéutica para la prevención y/o el tratamiento de condiciones mediadas por una actividad (especialmente inapropiada) de la renina, y a una composición farmacéutica para utilizarse en condiciones mediadas por una actividad (especialmente inapropiada) de la renina, la cual comprende un compuesto de la Fórmula I, o una sal farmacéuticamente aceptable del mismo, en asociación con un diluyente o material de vehículo farmacéuticamente aceptable para el mismo.

La presente invención proporciona además un método para la prevención y/o el tratamiento de condiciones mediadas por una actividad (especialmente inapropiada) de la renina, el cual comprende administrar una cantidad terapéuticamente efectiva de un compuesto de la presente invención a un animal de sangre

caliente, en especial un ser humano, que necesite dicho tratamiento.

Una dosificación unitaria para un mamífero de aproximadamente 50 a 70 kilogramos, puede contener entre aproximadamente 1 miligramo y 1,000 miligramos, convenientemente entre aproximadamente 5 y 600 miligramos del ingrediente activo. La dosificación terapéuticamente efectiva del compuesto activo depende de la especie de animal de sangre caliente (en especial un mamífero, más especialmente un ser humano), del peso corporal, de la edad, y de la condición individual, de la forma de administración, y del compuesto involucrado.

De conformidad con lo anterior, la presente invención también proporciona un producto farmacéutico que comprende una combinación terapéutica, por ejemplo un estuche, un estuche de partes, por ejemplo para utilizarse en cualquier método definido en la presente, el cual comprende un compuesto de la Fórmula I, o una sal farmacéuticamente aceptable del mismo, para utilizarse de una manera concomitante o en secuencia con cuando menos una composición farmacéutica que comprenda cuando menos otro agente terapéutico, de preferencia seleccionado a partir de agentes anti-diabéticos, agentes hipolipidémicos, agentes contra la obesidad, o agentes anti-hipertensivos. El estuche terapéutico puede comprender instrucciones para su administración.

De una manera similar, la presente invención proporciona

un estuche de partes que comprende: (i) una composición farmacéutica que comprende un compuesto de la Fórmula I de acuerdo con la invención; y (ii) una composición farmacéutica que comprende un compuesto seleccionado a partir de un anti-diabético, un agente hipolipidémico, un agente contra la obesidad, un agente anti-hipertensivo, o una sal farmacéuticamente aceptable de los mismos, en la forma de dos unidades separadas de los componentes (i) a (ii).

De la misma manera, la presente invención proporciona un método como se define anteriormente, el cual comprende la co-administración, por ejemplo de una manera concomitante o en secuencia, de una cantidad terapéutica-mente efectiva de un compuesto de la Fórmula I, o una sal farmacéuticamente aceptable del mismo, y cuando menos una segunda sustancia de fármaco, siendo esta segunda sustancia de fármaco de preferencia un anti-diabético, un agente hipolipidémico, un agente contra la obesidad, o un agente anti-hipertensivo, por ejemplo como se indica anteriormente.

De preferencia, se administra un compuesto de la invención a un mamífero que lo necesite.

De una manera preferible, se utiliza un compuesto de la invención para el tratamiento de una enfermedad que responda a la modulación de la actividad (especialmente inapropiada) de la renina.

Preferiblemente, la condición asociada con la actividad

(especialmente inapropiada) de la renina se selecciona a partir de hipertensión, ateroesclerosis, síndrome coronario inestable, insuficiencia cardíaca congestiva, hipertrofia cardíaca, fibrosis cardíaca, cardiomiopatía posterior a infarto, síndrome coronario inestable, disfunción diastólica, enfermedad crónica del riñón, fibrosis hepática, complicaciones resultantes de diabetes, tales como nefropatía, vasculopatía, y neuropatía, enfermedades de los vasos coronarios, restenosis en seguida de angioplastía, presión intraocular elevada, glaucoma, crecimiento vascular anormal, y/o hiperaldosteronismo, y/o además, deterioro cognoscitivo, enfermedad de Alzheimer, demencia, estados de ansiedad, y trastornos cognoscitivos.

Finalmente, la presente invención proporciona un método o uso, el cual comprende administrar un compuesto de la Fórmula I en combinación con una cantidad terapéuticamente efectiva de un agente anti-diabético, un agente hipolipidémico, un agente contra la obesidad, o un agente anti-hipertensivo.

Por último, la presente invención proporciona un método o uso, el cual comprende administrar un compuesto de la Fórmula I en la forma de una composición farmacéutica como se describe en la presente.

Las propiedades anteriormente citadas se pueden demostrar en pruebas *in vitro* e *in vivo*, empleando convenientemente mamíferos, por ejemplo ratones, ratas, conejos, perros, monos, u órganos aislados, tejidos y preparaciones de los mismos. Estos

compuestos se pueden aplicar *in vitro* en la forma de soluciones, por ejemplo de preferencia soluciones acuosas, e *in vivo*, ya sea enteralmente, parenteralmente, de una manera conveniente intravenosamente, por ejemplo como una suspensión o en una solución acuosa. El nivel de concentración *in vitro* puede estar en el intervalo de concentraciones de entre aproximadamente 10^{-3} molar y 10^{-10} molar. Una cantidad terapéuticamente efectiva *in vivo* puede estar en el intervalo, dependiendo de la vía de administración, de entre aproximadamente 0.001 y 500 miligramos/kilogramo, de preferencia de entre aproximadamente 0.1 y 100 miligramos/ kilogramo.

Como se describió anteriormente, los compuestos de la presente invención tienen propiedades inhibidoras de enzimas. En particular, inhiben la acción de la enzima renina natural. La renina pasa desde los riñones hacia la sangre, en donde efectúa la disociación del angiotensinógeno, liberando el decapéptido de angiotensina I, que luego se disocia en los pulmones, los riñones, y otros órganos, para formar el octapéptido de angiotensina II. El octapéptido aumenta la presión sanguínea tanto directamente mediante vasoconstricción arterial, como indirectamente mediante la liberación desde las glándulas adrenales de la hormona de retención de iones de sodio, aldosterona, acompañado esto por un aumento en el volumen de fluido extracelular, cuyo aumento se puede atribuir a la acción de la angiotensina II. Los inhibidores de la actividad enzimática de la renina conducen a una reducción en

la formación de angiotensina I, y en consecuencia, se produce una cantidad más pequeña de angiotensina II. La concentración reducida de esta hormona peptídica activa es una causa directa del efecto hipotensivo de los inhibidores de renina.

La acción de los inhibidores de renina se puede demostrar, entre otras cosas, experimentalmente, por medio de pruebas *in vitro*, midiéndose la reducción en la formación de la angiotensina I en diferentes sistemas (plasma humano, renina humana purificada junto con sustrato de renina sintético o natural).

Se pueden emplear, entre otras cosas, las siguientes pruebas *in vitro*:

Se incuba la renina humana recombinante (expresada en células de Ovario de Hámster Chino, y purificada empleando métodos convencionales) en una concentración de 7.5 nM, con el compuesto de prueba en diferentes concentraciones durante 1 hora a temperatura ambiente, en regulador de Tris-HCl 0.1 M, pH de 7.4, conteniendo NaCl 0.05 M, EDTA 0.5 mM, y CHAPS al 0.05 por ciento. Se agrega el sustrato de péptido sintético Arg-Glu(EDANS)-Ile-His-Pro-Phe-His-leu-Val-Ile_His_Thr-Lys (DABCYL)-Arg9 hasta una concentración final de 2 µM, y se registra el aumento en la fluorescencia a una longitud de onda de excitación de 350 nanómetros, y a una longitud de onda de emisión de 500 nanómetros, en un espectro-fluorímetro de microplaca. Los valores IC_{50} se calculan a partir del porcentaje de inhibición de la actividad de renina como una función de la concentración del

compuesto de prueba (Transferencia de Energía con Resonancia de Fluorescencia, FRET, ensayo). Los compuestos de la Fórmula I, en este ensayo, de preferencia pueden mostrar valores IC_{50} en el intervalo de 1 nM a 20 µM.

De una manera alternativa, la renina humana recombinante (expresada en células de Ovario de Hámster Chino y purificada empleando métodos convencionales) en una concentración de 0.5 nM, se incuba con el compuesto de prueba en diferentes concentraciones durante 2 horas a 37°C, en regulador de Tris-HCl 0.1 M, pH de 7.4, conteniendo NaCl 0.05 M, EDTA 0.5 mM, y CHAPS al 0.05 por ciento. Se agrega el sustrato de péptido sintético Arg-Glu(EDANS)-Ile-His-Pro-Phe-His-leu-Val-Ile_His_Thr-Lys(DABCYL)-Arg9 hasta una concentración final de 4 µM, y se registra el aumento en la fluorescencia a una longitud de onda de excitación de 340 nanómetros, y a una longitud de onda de emisión de 485 nanómetros, en un espectro-fluorímetro de microplaca. Los valores IC_{50} se calculan a partir del porcentaje de inhibición de la actividad de renina como una función de la concentración del compuesto de prueba (Transferencia de Energía con Resonancia de Fluorescencia, FRET, ensayo). Los compuestos de la Fórmula I, en este ensayo, de preferencia pueden mostrar valores IC_{50} en el intervalo de 1 nM a 20 µM.

En otro ensayo, se incuba plasma humano salpicado con renina humana recombinante (expresada en células de Ovario de Hámster Chino, y purificada empleando métodos convencionales)

en una concentración de 0.8 nM, con el compuesto de prueba en diferentes concentraciones durante 2 horas a 37°C, en Tris/HCl 0.1 M, pH de 7.4, conteniendo NaCl 0.05 M, EDTA 0.5 mM, y CHAPS al 0.025 por ciento (peso/ volumen). Se agrega el sustrato de péptido sintético Ac-Ile-His-Pro-Phe-His-Leu-Val-Ile-His-Asn-Lys-[DY-505-X5] hasta una concentración final de 2.5 µM. La reacción enzimática se detiene mediante la adición de un exceso de un inhibidor de bloqueo. El producto de la reacción se separa mediante electroforesis capilar, y se cuantifica mediante medición espectrofotométrica a una longitud de onda de 505 nanómetros. Los valores IC_{50} se calculan a partir del porcentaje de inhibición de la actividad de renina como una función de la concentración del compuesto de prueba. Los compuestos de la Fórmula I, en este ensayo, de preferencia pueden mostrar valores IC_{50} en el intervalo de 1 nM a 20 µM.

En otro ensayo, se incuba la renina humana recombinante (expresada en células de Ovario de Hámster Chino, y purificada empleando métodos convencionales) en una concentración de 0.8 nM, con el compuesto de prueba en diferentes concentraciones durante 2 horas a 37°C, en Tris/HCl 0.1 M, pH de 7.4, conteniendo NaCl 0.05 M, EDTA 0.5 mM, y CHAPS al 0.025 por ciento (peso/volumen). Se agrega el sustrato de péptido sintético Ac-Ile-His-Pro-Phe-His-Leu-Val-Ile-His-Asn-Lys-[DY-505-X5] hasta una concentración final de 2.5 µM. La reacción enzimática se detiene mediante la adición de un exceso de un inhibidor de bloqueo. El

producto de la reacción se separa mediante electroforesis capilar, y se cuantifica mediante medición espectrofotométrica a una longitud de onda de 505 nanómetros. Los valores IC_{50} se calculan a partir del porcentaje de inhibición de la actividad de renina como una función de la concentración del compuesto de prueba. Los compuestos de la Fórmula I, en este ensayo, de preferencia muestran valores IC_{50} en el intervalo de 1 nM a 20 µM.

En los animales deficientes en sal, los inhibidores de renina provocan una reducción en la presión sanguínea. La renina humana puede diferir de la renina de otras especies. Con el objeto de probar los inhibidores de la renina humana, se pueden utilizar primates, por ejemplo titíes (*Callithrix jacchus*), debido a que la renina humana y la renina de primate son sustancialmente homólogas en la región enzimáticamente activa. Entre otras, se pueden utilizar las siguientes pruebas *in vivo*.

Los compuestos de la Fórmula I se pueden probar *in vivo* en primates, como se describe en la literatura (ver, por ejemplo, Schnell C. R. y colaboradores, Measurement of blood pressure and heart rate by telemetry in conscious, unrestrained marmosets, Am. J. Physiol. 264 (Heart Circ. Physiol. 33). 1993:1509-1516; ó Schnell C. R. y colaboradores, Measurement of blood pressure, heart rate, body temperature, ECG and activity by telemetry in conscious, unrestrained marmosets. Memorias del quinto simposio de FELASA: Welfare and Science. Eds. BRIGHTON. 1993.

Los siguientes ejemplos, aunque representan las

modalidades preferidas de la invención, sirven para ilustrar la invención sin limitar su alcance:

Abreviaturas

abs.	Absoluto.
Ac	Acetilo.
AcOEt	Acetato de etilo.
AcOH	Ácido acético.
aq.	Acuoso.
Bz	Bencilo.
cc	Concentrado.
c-hexano	Ciclohexano.
DIBAL-H	Hidruro de di-isobutil-aluminio.
DMF	Dimetil-formamida.
DMSO	Sulfóxido de dimetilo.
DPPA	Difenil-fosforil-azida.
EDCI	Clorhidrato de 1-(3-dimetil-amino-propil)-3-etil-carbodi-imida.
Éter	Dietil-éter.
Et_3N	Trietil-amina.
Et_2O	Dietil-éter.
EtOH	Etanol.
Flujo	Velocidad de flujo.
h	Hora(s).
HMPA	Hexametil-fosforamida.

HOBt	1-hidroxi-7-benzotriazol.
HPLC	Cromatografía de líquidos de alto rendimiento.
iPrOH	Isopropanol.
L	Litro(s).
KHMDS	Hexametil-disilazano de potasio.
LC-MS	Cromatografía de líquidos/Espectrometría de masas.
LDA	Di-isopropil-amina de litio.
Me	Metilo.
MeI	Yoduro de metilo.
MeOH	Metanol.
MesCl	Cloruro de metansulfonilo.
Min	Minuto(s).
mL	Mililitro(s).
EM	Espectrometría de masas.
NMM	4-metil-morfolina.
RMN	Resonancia Magnética Nuclear.
Pd/C	Paladio sobre carbón.
Ph	Fenilo.
PyBOP	Hexafluorofosfato de (benzotriazol-1-iloxi)-tripirrolidino-fosfonio.
RT	Temperatura ambiente.
TBAF	Fluoruro de tetra-butil-amonio.
TBDMS-Cl	Cloruro de terbutil-dimetil-sililo.
TBDMS	Terbutil-dimetil-sililo.

TBME Terbutil-metil-éter.

TEA Trietil-amina.

TEMPO Radical libre de 2,2,6,6-tetrametil-1-piperidiniloxilo.

TFA Ácido trifluoroacético.

THF Tetrahidrofurano.

RP Fase inversa.

Prep Preparación.

sat. Saturado.

TLC Cromatografía de capa delgada.

t_r Tiempo de retención.

Marcas Comerciales Registradas

Celite = Celite® (The Celite Corporation) = auxiliar de filtración basado en tierra diatomácea.

NH_2 Isolute = (= Isolute® NH_2, Isolute® está registrada para Argonaut Technologies, Inc.) = Intercambiador de iones con grupos amino basado en gel de sílice.

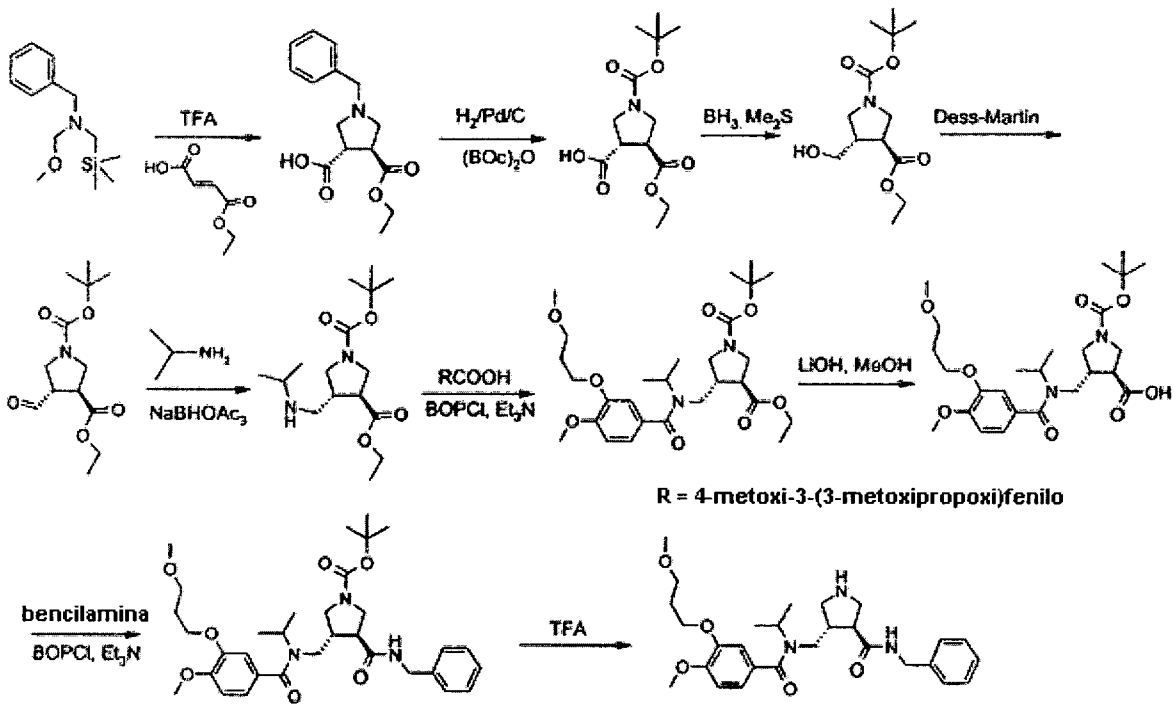
Nucleosil = Nucleosil®, marca comercial registrada de Machery & Nagel, Düren, FRG para materiales de HPLC.

Las temperaturas se miden en grados Celsius. A menos que se indique de otra manera, las reacciones tienen lugar a temperatura ambiente.

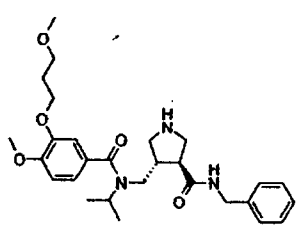
Condiciones de TLC:

Los valores R_f para la TLC se miden sobre placas de TLC de 5 x 10 centímetros, gel de sílice F_{254}, Merck, Darmstadt, Alemania.

Esquema de reacción 1



Ejemplo 1:Bencil-amida del ácido (3S*,4S*)-4-({iso-propil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-carboxílico.



A una solución de terbutil-éster del ácido (3S*,4R*)-3-

bencil-carbamoil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (61 miligramos, 0.098 milimoles) en 2 mililitros de CH_2Cl_2, se le agrega ácido trifluoroacético (113 microlitros, 1.46 milimoles). La mezcla se agita a 30°C durante 2 horas, luego durante la noche a temperatura ambiente, y se vierte en una solución saturada de $NaHCO_3$. Las capas se separan, y la acuosa se retro-extrae dos veces con CH_2Cl_2. Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran, y se concentran. El material crudo se purifica mediante cromatografía por evaporación instantánea sobre una columna de evaporación instantánea de NH_2 Isolute SPE Flash (eluyente: CH_2Cl_2:MeOH, de 100:0 a 95:5), para dar el producto del título. TLC, R_f (CH_2Cl_2/MeOH, 9:1) = 0.2. MS (LC-MS): 498 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 4.38 minutos.

A una solución de la base libre en dioxano (2 mili-litros), se le agrega HCl 4N en dioxano (0.105 milimoles, 26 microlitros), y la solución resultante se liofiliza para proporcionar la sal de clorhidrato correspondiente como un polvo blanco.

El material de inicio se prepara como sigue:

A. Mono-etil-éster del ácido (3S*,4S*)-1-bencil-pirrolidin-3,4-dicarboxílico

A una solución agitada de mono-etil-fumarato (2.85 gramos,

19.8 milimoles) y ácido trifluoro-acético (1.98 mili-moles, 0.15 mililitros) en cloruro de metileno (50 mililitros), se le agrega N-bencil-N-(metoxi-metil)-trimetil-silil-amina (Aldrich) (9.41 gramos, 39.6 milimoles) a 0°C bajo N_2. La mezcla se agita a 0°C durante 30 minutos, y luego a temperatura ambiente durante 48 horas. El material crudo se concentra y se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente: CH_2Cl_2:MeOH, de 85:15 a 85:15 + NH_4OH al 2 por ciento), para dar el compuesto del título. MS (LC-MS): 278.0 $[M+H]^+$; ^{1}H-RMN (CD_3OD, 400 MHz): δ 1.29 (t, 3H), 3.28 (m, 5H), 3.60 (m, 1H), 4.07 (m, 2H), 4.20 (m, 2H), 4.20 (m, 2H), 7.47 (m, 5H) ppm.

B. 3-etil-éster de 1-terbutil-éster del ácido (3S*,4S*)-pirrolidin-1,3,4-tricarboxílico

Una mezcla de mono-etil-éster del ácido (3S*,4S*)-1-bencil-pirrolidin-3,4-dicarboxílico (10 gramos, 36.1 mili-moles), carbonato de diterbutilo (7.9 gramos, 39.6 milimoles) y $Pd(OH)_2/C$ al 20 por ciento (1 gramo, 50 por ciento húmedo) en EtOH (200 mililitros), se agita bajo una atmósfera de hidrógeno durante 5 horas. El material crudo se filtra sobre un cojín de Celite, y se concentra. La ^{1}H-RMN indica que el compuesto del título se obtiene limpiamente. TLC, R_f (AcOEt) = 0.17. MS (LC-MS): 286.1 $[M-H]^-$.

C. 3-etil-éster de 1-terbutil-éster del ácido (3S*,4S*)-4-hidroxi-metil-pirrolidin-1,3-dicarboxílico

A una solución de 3-etil-éster de 1-terbutil-éster del ácido (3S*,4S*)-pirrolidin-1,3,4-tricarboxílico (10 gramos, 34.8 milimoles)

en tetrahidrofurano (180 mililitros), se le agrega lentamente una solución de complejo de borano-sulfuro de dimetilo (2N en tetrahidrofurano, 24.4 mililitros, 48.7 milimoles) a -10°C. La mezcla se agita a -10°C durante 20 minutos, luego se deja llegar a la temperatura ambiente, y se agita adicionalmente durante 4 horas. Se agrega con cuidado MeOH (¡exotérmico!), y la mezcla se concentra bajo presión reducida. Nuevamente se agrega MeOH, y la mezcla se concentra. Esta operación se repite 3 veces, y luego la mezcla finalmente se recupera en una solución acuosa saturada de $NaHCO_3$, y se extrae 3 veces con CH_2Cl_2. Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran, y se concentran. El material crudo se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente: CH_2Cl_2:MeOH, de 100:0 a 95:5), para dar el compuesto del título como el producto. TLC, R_f (AcPEt = 0.52. MS (LC-MS): 174.1 $[M+H-Boc]^+$.

D. 3-etil-éster de 1-terbutil-éster del ácido (3S*,4S*)-4-formil-pirrolidin-1,3-dicarboxílico

A una mezcla bien agitada del 3-etil-éster del 1-terbutil-éster del ácido (3S*,4S*)-4-hidroxi-metil-pirrolidin-1,3-dicarboxílico (3.21 gramos, 11.74 milimoles) y peryodinano Dess-Martin (2.63 gramos, 11.74 milimoles) en CH_2Cl_2 (30 mililitros), se le agrega CH_2Cl_2 húmedo (232 microlitros de agua en 10 mililitros de CH_2Cl_2). La solución transparente llega a hacerse nebulosa hacia el final de la adición de CH_2Cl_2 húmedo. La mezcla se diluye con

Et_2O, luego se concentra hasta unos cuantos mililitros de solvente mediante evaporación giratoria. El residuo se recupera en Et_2O, y luego se lava con 1:1 de $Na_2S_2O_3$ al 10 por ciento: $NaHCO_3$ acuoso saturado, seguido por H_2O y salmuera. Los lavados acuosos se retro-extraen con Et_2O, y esta capa orgánica se lava con H_2O y salmuera. Las capas orgánicas combinadas se secan con Na_2SO_4, se filtran, y se concentran. La mezcla cruda se utiliza en el siguiente paso sin mayor purificación. TLC, R_f (ciclo-hexano/AcOEt, 8:2) = 0.2.

E. 3-etil-éster de 1-terbutil-éster del ácido (3S*,4R*)-4-(isopropil-amino-metil)-pirrolidin-1,3-dicarboxílico

Una solución del 3-etil-éster de 1-terbutil-éster del ácido (3S*,4R*)-4-(isopropil-amino-metil)-pirrolidin-3-di-carboxílico (2.87 gramos, 10.56 milimoles) e isopropil-amina (2.72 mililitros, 31.68 milimoles) en 1,2-dicloroetano (150 mililitros) se agita durante 25 minutos, antes de que siga la adición de $NaBH(OAc)_3$ (3.12 gramos, 14.78 milimoles). La solución se agita durante 4 horas, luego se diluye con CH_2Cl_2, y se lava con una solución acuosa saturada de $NaHCO_3$. Los extractos orgánicos combinados se secan sobre Na_2SO_4, y se concentran. El material crudo se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente: CH_2Cl_2/MeOH, de 100:0 a 80:20), para dar el producto del título. TLC, R_f (CH_2Cl_2/MeOH, 95:5) = 0.1.

F. 3-etil-éster de 1-terbutil-éster del ácido (3S*,4R*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-

metil)-pirrolidin-1,3-dicarboxílico

Una mezcla del 3-etil-éster de 1-terbutil-éster del ácido (3S*,4R*)-4-(isopropil-amino-metil)-pirrolidin-1,3-di-carboxílico (2.58 gramos, 8.2 milimoles), ácido 3-(3-metoxi-propoxi)-4-metoxi-benzoico (1.93 gramos, 8.04 milimoles), cloruro de bis-(2-oxo-3-oxazolidinil)-fosfínico (2.3 gramos, 9.02 milimoles) y trietil-amina (4.57 microlitros, 32.81 mili-moles) en CH_2Cl_2 (50 mililitros), se pone a reflujo durante 2 horas, y luego se apaga mediante la adición de una solución acuosa de $NaHCO_3$. La capa orgánica se separa, y la fase acuosa se extrae 3 veces con AcOEt. Los extractos orgánicos combinados se secan (Na_2SO_4), y el solvente se retira al vacío. El producto crudo se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente: ciclo-hexano/AcOEt, de 50:50 a 0:100, y luego AcOEt/MeOH, 95:5), para dar el producto del título. TLC, R_f (CH_2Cl_2/MeOH, 95:5) = 0.3. t_R (HPLC, columna C18, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.76 minutos.

G. 1-terbutil-éster del ácido (3S*,4R*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1,3-dicarboxílico

A una solución del 3-etil-éster de 1-terbutil-éster del ácido (3S*,4R*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1,3-dicarboxílico (1.41 gramos, 2.63

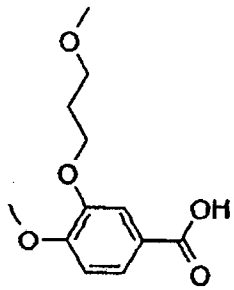
milimoles) en MeOH (25 mililitros), enfriada a 0°C, se le agregan 662 miligramos de $LiOH \cdot H_2O$. La mezcla de reacción se agita durante la noche. La mezcla se recupera en CH_2Cl_2, se agrega una solución acuosa de HCl (al 5 por ciento), y la mezcla resultante se extrae 3 veces con CH_2Cl_2, se seca sobre Na_2SO_4, se filtra, y se concentra. El material crudo se utiliza en el siguiente paso sin purificación. TLC, R_f (CH_2Cl_2/MeOH, 95:5) = 0.15. MS (LC-MS): 409.0 $[M-H-Boc]^-$; t_R (HPLC, columna C18, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 4.96 minutos.

H. Terbutil-éster del ácido (3S*,4R*)-3-bencil-carbamoil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1,3-carboxílico

A una solución en agitación del 1-terbutil-éster del ácido (3S*,4R*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1,3-dicarboxílico (70 mili-gramos, 0.138 milimoles), cloruro de bis-(2-oxo-3-oxazolidinil)-fosfínico (42 miligramos, 0.166 milimoles), y trietil-amina (77 microlitros, 0.552 milimoles) en CH_2Cl_2 (3 mililitros), se le agrega bencil-amina (18 microlitros, 0.166 milimoles). La solución resultante se pone a reflujo durante 2 horas, y luego se apaga mediante la adición de una solución acuosa de $NaHCO_3$. La capa orgánica se separa, y la fase acuosa se extrae 3 veces con CH_2Cl_2. Los extractos orgánicos combinados se secan (Na_2SO_4), y el solvente se retira al vacío. El

material crudo se purifica mediante HPLC de preparación (C18-OBD-AQ, 5 micras, 20 x 50 milímetros, YMC, eluyente: CH_3CN/H_2O + HCOOH al 0.1 por ciento, flujo: 20 mililitros/minuto). Las fracciones de la HPLC se recolectan y se liofilizan para proporcionar el producto del título. TLC, R_f (CH_2Cl_2/MeOH, 95:5) = 0.2. MS (LC-MS): 598.0 $[M+H]^+$; t_R (HPLC, columna C18, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.60 minutos.

Ácido 4-metoxi-3-(3-metoxi-propoxi)-benzoico



a. Metil-éster del ácido 4-metoxi-3-(3-metoxi-propoxi)-benzoico

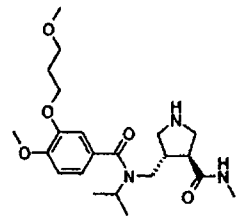
Una solución de 3-hidroxi-4-metoxi-benzoato de metilo (Aldrich) (89.3 gramos, 0.49 moles), K_2CO_3 (100.5 gramos, 0.727 moles), y 1-bromo-3-metoxi-propano (80 gramos, 0.523 moles) en CH_3CN (1100 mililitros), se pone a reflujo durante 6 horas. Después de terminarse la reacción, la mezcla se enfría a temperatura ambiente, y se concentra bajo presión reducida. El residuo se recupera en AcOEt (500 mililitros), y se lava con agua. La capa acuosa se retro-extrae dos veces con AcOEt, y los

extractos orgánicos combinados se secan sobre $MgSO_4$, se filtran, y se concentran, para proporcionar el compuesto del título, el cual se utiliza adicionalmente en el siguiente paso sin purificación. t_R (HPLC, CC 70/4 columna Nucleosil 3 C18HD, del 20 al 100 por ciento de CH_3CN en H_2O en 2 minutos, luego 4 minutos con el 100 por ciento de CH_3CN; CH_3CN y H_2O con ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 3.07 minutos.

b. Ácido 4-metoxi-3-(3-metoxi-propoxi)-benzoico

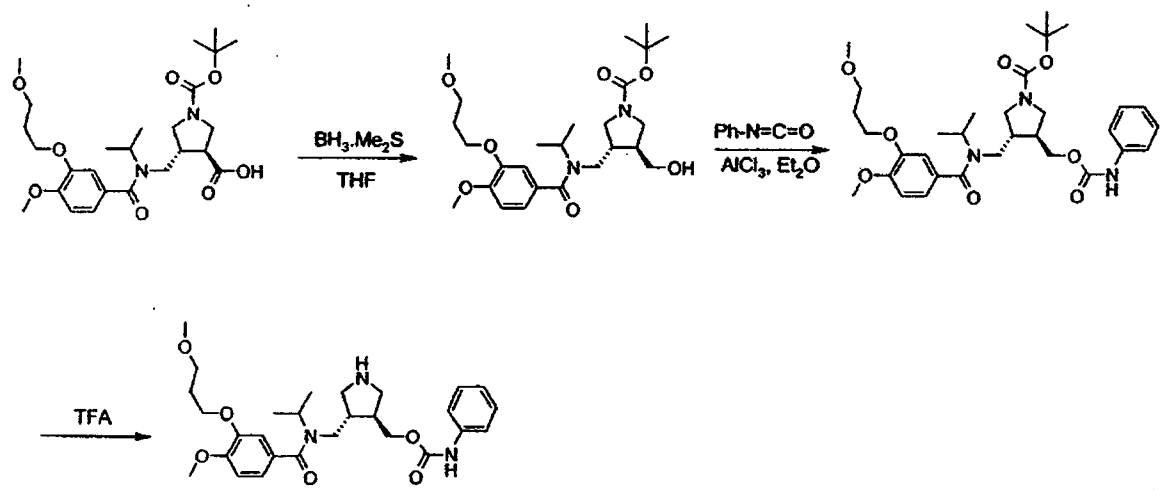
Una solución de metil-éster del ácido 4-metoxi-3-(3-metoxi-propoxi)-benzoico (140 gramos, 0.55 moles) y NaOH (1N, 825 mililitros, 0.825 moles) en MeOH (840 mili-litros), se agita a temperatura ambiente durante 18 horas. Después de terminar, el solvente se retira bajo presión reducida, y el residuo se diluye con agua (200 mililitros) y se extrae dos veces con AcOEt (250 mililitros). La capa acuosa se acidifica mediante la adición de HCl acuoso (2N, 470 mili-litros), y se extrae 3 veces con AcOEt (1 litro). Los extractos orgánicos combinados se lavan con salmuera, se secan sobre Na_2SO_4, se filtran, y se concentran. El material crudo se purifica mediante cristalización en AcOEt, para dar el compuesto del título. MS (LC-MS): 239.1 $[M-H]^-$; t_R (HPLC, CC 70/4, columna Nucleosil 3 C18HD, del 20 al 100 por ciento de CH_3CN en H_2O en 2 minutos, luego 4 minutos con el 100 por ciento de CH_3CN; CH_3CN y H_2O con ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 2.43 minutos.

Ejemplo 2: Metil-amida del ácido (3S*,4R*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1,3-carboxílico



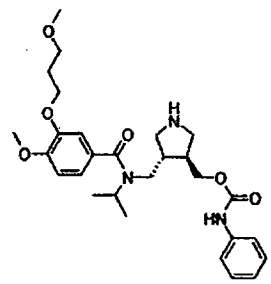
El compuesto del título se prepara de una manera análoga a la descrita para el compuesto del título del Ejemplo 1, empezando a partir de 1-terbutil-éster del ácido (3S*,4R*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1,3-dicarboxílico. MS (LC-MS): 422.1 $[MH]^+$; t_R (HPLC, columna Nucleosil C18, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, flujo: 1.5 mililitros/minuto): 3.83 minutos.

Esquema de reacción 2



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Ejemplo 3: (3S*,4S*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil-éster del ácido fenil-carbámico



A una solución del terbutil-éster del ácido (3S*,4S*)-3-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-4-fenil-carbamoiloxi-metil-pirrolidin-1-carboxílico (68 miligramos, 0.11 milimoles) en 2 mililitros de CH_2Cl_2, se le agrega ácido trifluoroacético (128 microlitros, 1.66 milimoles). La mezcla se agita a 30°C durante 2 horas, luego durante la noche a temperatura ambiente, y se vierte en una solución saturada de $NaHCO_3$. Las capas se separan, y la acuosa se retro-extrae dos veces con CH_2Cl_2. Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran, y se concentran. El material crudo se purifica mediante cromatografía por evaporación instantánea sobre una columna de NH_2 Isolute SPE Flash (eluyente: CH_2Cl_2/ MeOH, de 100:0 a 97:3), para dar el producto del título. MS (LC-MS): 514.0 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 4.52 minutos.

A una solución de la base libre en dioxano (2 mili-litros), se le agrega HCl 4N en dioxano (0.099 milimoles, 25 microlitros), y la solución resultante se liofiliza para proporcionar la sal de clorhidrato correspondiente como un polvo blanco.

El material de inicio se prepara como sigue:

A. Terbutil-éster del ácido (3S*,4R*)-3-hidroximetil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico.

A una solución del terbutil-éster del ácido (3S*,4R*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1,3-dicarboxílico (1.29 gramos, 2.54 milimoles) (Ejemplo 1G) en tetrahidrofurano (25 mililitros), se le agrega lentamente una solución de complejo de borano-sulfuro de dimetilo (2M en tetrahidrofurano, 2.80 mililitros, 5.58 milimoles) a -10°C. La mezcla se agita durante 20 minutos a -10°C, luego se deja alcanzar la temperatura ambiente, y se agita adicionalmente durante la noche. Se agrega cuidadosamente MeOH (¡exotérmico!), y la mezcla se concentra bajo presión reducida. Se agrega nuevamente MeOH, y la mezcla se concentra. Esta operación se repite 3 veces, y la mezcla finalmente se recupera en una solución acuosa saturada de $NaHCO_3$, y se extrae 3 veces con CH_2Cl_2. Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran, y se concentran. El material crudo se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente: CH_2Cl_2/MeOH, de 100:0 a 95:5), para dar el producto

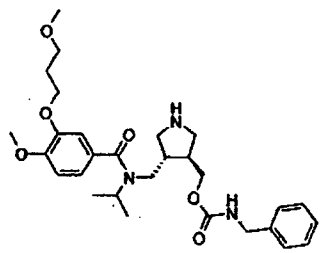
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deseado. TLC, R_f (CH_2Cl_2/ MeOH, 95:5) = 0.3. MS (LC-MS): 395.1 $[M+H-Boc]^+$; t_R (HPLC, columna C18, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.01 minutos.

B. Terbutil-éster del ácido (3R*,4S*)-3-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-4-fenil-carbamoiloxi-metil-pirrolidin-1-carboxílico.

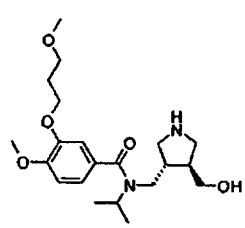
Se agregan isocianato de fenilo (44 microlitros, 0.404 milimoles), seguido por $AlCl_3$ (27 miligramos, 0.202 milimoles) a una solución de terbutil-éster del ácido (3S*,4R*)-3-hidroxi-metil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (100 miligramos, 0.202 milimoles) en Et_2O (6 mililitros). La mezcla resultante se agita a temperatura ambiente durante la noche. Para el procesamiento, se agrega una solución saturada de $NaHCO_3$, y la mezcla se extrae con acetato de etilo. Los extractos combinados se secan (Na_2SO_4), y el solvente se evapora. El producto crudo se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente: ciclo-hexano/AcOEt, de 80:20 a 0:100), para dar el producto del título. TLC, R_f (CH_2Cl_2/ MeOH, 95:5) = 0.5. MS (LC-MS): 514.0 $[M+H-Boc]^+$; t_R (HPLC, columna C18, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.91 minutos.

Ejemplo 4:(3S*,4S*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil-éster del ácido bencil-carbámico.



El compuesto del título se prepara de una manera análoga a la descrita en el Ejemplo 3, a partir del terbutil-éster del ácido (3S*,4R*)-3-hidroxi-metil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico e isocianato de bencilo. MS (LC-MS): 528.3 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 4.52 minutos.

Ejemplo 5:N-(3S*,4S*)-4-hidroxi-metil-pirrolidin-3-ilmetil)N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida.

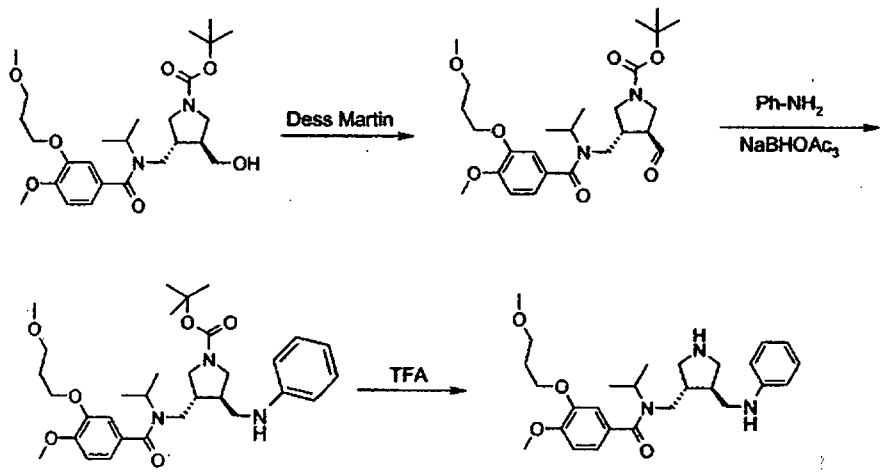


A una solución del terbutil-éster del ácido (3S*,4R*)-3-

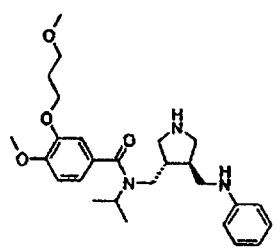
hidroxi-metil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (85 miligramos, 0.172 milimoles), en 2 mililitros de CH_2Cl_2, se le agrega ácido trifluoroacético (85 microlitros, 2.23 milimoles). La mezcla se agita durante 4.5 horas a temperatura ambiente, y se vierte en una solución saturada de $NaHCO_3$. Las capas se separan, y la acuosa se retro-extrae dos veces con CH_2Cl_2. Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran, y se concentran. El material crudo se purifica mediante cromatografía por evaporación instantánea sobre una columna de NH_2 Isolute SPE Flash (eluyente: CH_2Cl_2/MeOH, de 100:0 a 99:1), para dar el producto del título. MS (LC-MS): 395.1 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 3.75 minutos.

A una solución de la base libre en dioxano (2 mili-litros), se le agrega HCl 4N en dioxano (0.009 milimoles, 2.2 microlitros), y la solución resultante se liofiliza para proporcionar la sal de clorhidrato correspondiente como un polvo blanco.

Esquema de reacción 3



Ejemplo 6:N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-N-((3S*,4S*)-4-fenil-amino-metil-pirrolidin-3-ilmetil)-benzamida



A una solución del terbutil-éster del ácido (3R*,4R*)-3-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-4-fenil-amino-metil-pirrolidin-1-carboxílico (65 miligramos, 0.12 milimoles) en 2 mililitros de CH_2Cl_2, se le agrega ácido trifluoroacético (139 microlitros, 1.8 milimoles). La mezcla se agita durante 2 horas a temperatura ambiente. y se vierte en una solución saturada de $NaHCO_3$. Las capas se separan, y la acuosa se retro-extrae dos veces con CH_2Cl_2. Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran, y se concentran. El

material crudo se purifica mediante cromatografía por evaporación instantánea sobre una columna de NH_2 Isolute SPE Flash (eluyente: CH_2Cl_2/MeOH, de 100:0 a 97:3), para dar el producto del título. TLC, R_f (SiO_2-NH_2, CH_2Cl_2/ MeOH, 95:5) = 0.6. MS (LC-MS): 470.0 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 3.37 minutos.

A una solución de la base libre en dioxano (2 mili-litros), se le agrega HCl 4N en dioxano (0.242 milimoles, 60 microlitros), y la solución resultante se liofiliza para proporcionar la sal de diclorhidrato correspondiente como un polvo blanco.

El material de inicio se prepara como sigue:

A. Terbutil-éster del ácido (3S*,4R*)-3-formil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico.

A una mezcla bien agitada del terbutil-éster del ácido (3S*,4R*)-3-hidroxi-metil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (600 miligramos, 1.21 milimoles) y peryodinano de Dess-Martin (272 miligramos, 1.21 milimoles) en CH_2Cl_2 (10 mili-litros), se le agrega lentamente CH_2Cl_2 húmedo (24 microlitros de agua en 2 mililitros de CH_2Cl_2). La solución transparente se hace nebulosa hacia el final de la adición de CH_2Cl_2 húmedo. La mezcla se diluye con

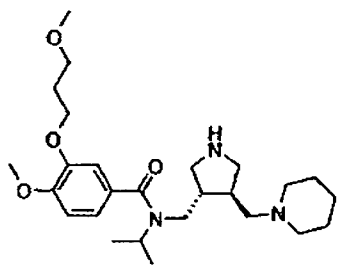
Et_2O y se concentra hasta unos cuantos mililitros de solvente mediante evaporación giratoria. El residuo se recupera en Et_2O, y se lava con 1:1 de $Na_2S_2O_3$/solución acuosa saturada de $NaHCO_3$, seguido por H_2O y salmuera. Los lavados acuosos se retro-extraen con Et_2O, y esta capa orgánica se lava con H_2O y salmuera. Las capas orgánicas combinadas se secan sobre Na_2SO_4, se filtran, y se concentran bajo presión reducida. El material crudo se utiliza sin mayor purificación en el siguiente paso. TLC, R_f (CH_2Cl_2/ MeOH, 95:5) = 0.3. t_R (HPLC, columna Nucleosil C18, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.16 minutos.

B. Terbutil-éster del ácido (3R*,4R*)-3-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-4-fenil-amino-metil-pirrolidin-1-carboxílico.

Una solución del terbutil-éster del ácido (3S*,4R*)-3-formil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (100 miligramos, 0.20 milimoles) y anilina (26 microlitros, 0.28 milimoles) en 1,2-dicloro-etano (5 mililitros), se agita durante 25 minutos, antes de que siga la adición de $NaBH(OAc)_3$ (60 miligramos, 0.28 milimoles). La solución se agita durante la noche a temperatura ambiente, luego se diluye con CH_2Cl_2, y se lava con una solución acuosa saturada de $NaHCO_3$. Los extractos orgánicos combinados se secan sobre Na_2SO_4, y se

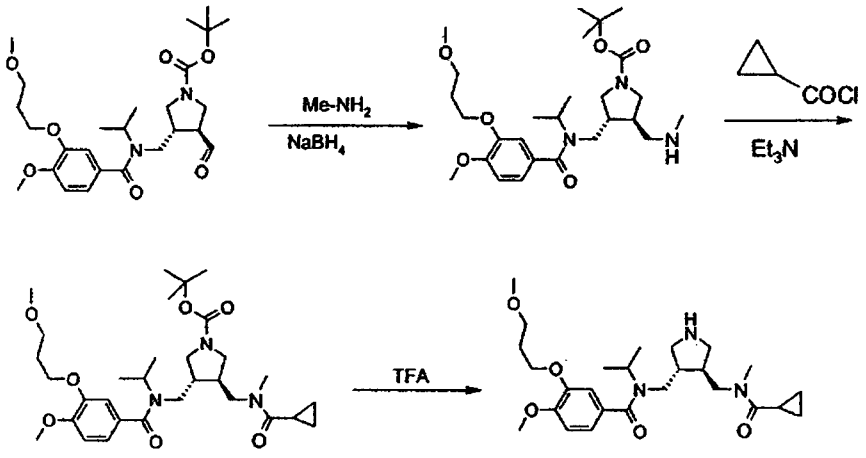
concentran. El material crudo se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente: CH_2Cl_2/MeOH, de 100:0 a 97:3), para dar el producto del título. TLC, R_f (CH_2Cl_2/MeOH, 95:5) = 0.25. MS (LC-MS): 570.0 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.31 minutos.

Ejemplo 7:N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-N-((3S*,4S*)-4-piperidin-1-ilmetil-pirrolidin-3-ilmetil)-benzamida.

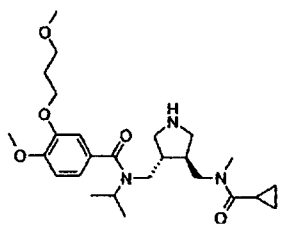


El compuesto del título se prepara de una manera análoga a la descrita en el Ejemplo 5, a partir del terbutil-éster del ácido (3S*,4R*)-3-formil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico. MS (LC-MS): 462.1 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 3.74 minutos.

Esquema de reacción 4



Ejemplo 8:N-{(3S*,4S*)-4-[(ciclopropan-carbonil-metil-amino)-metil]-pirrolidin-3-ilmetil}-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida



A una solución del terbutil-éster del ácido (3R*,4R*)-3-[(ciclopropan-carbonil-metil-amino)-metil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (154 miligramos, 0.267 mili-moles) en 3 mililitros de CH_2Cl_2, se le agrega ácido trifluoro-acético (309 microlitros, 4.01 milimoles). La mezcla se agita durante 4 horas a temperatura ambiente, y se vierte en una solución saturada de $NaHCO_3$. Las capas se separan, y la acuosa se retro-extrae dos veces con CH_2Cl_2. Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran, y se

concentran. El material crudo se purifica mediante cromatografía por evaporación instantánea sobre una columna de NH_2 Isolute SPE Flash (eluyente: CH_2Cl_2/MeOH, de 100:0 a 95:5), para dar el producto del título. TLC, R_f (SiO_2-NH_2, CH_2Cl_2/ MeOH, 95:5) = 0.1. MS (LC-MS): 476.1 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 4.10 minutos.

A una solución de la base libre en dioxano (2 mili-litros), se le agrega HCl 4N en dioxano (0.198 milimoles, 50 microlitros), y la solución resultante se liofiliza, para proporcionar la sal de diclorhidrato correspondiente como un polvo blanco.

El material de inicio se prepara como sigue:

A. Terbutil-éster del ácido (3R*,4R*)-3-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-4-metil-amino-metil-pirrolidin-1-carboxílico.

A una solución del terbutil-éster del ácido (3S*,4R*)-3-formil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (150 miligramos, 0.304 milimoles) y sulfato de magnesio (92 mili-gramos, 0.373 milimoles) en tetrahidrofurano (4 mililitros), se le agrega metil-amina (1.52 mililitros, 3.044 milimoles, 2M en tetrahidrofurano). La solución se agita a temperatura ambiente durante la noche bajo una atmósfera de nitrógeno, y se le agrega $NaBH_4$ (23 miligramos, 0.608

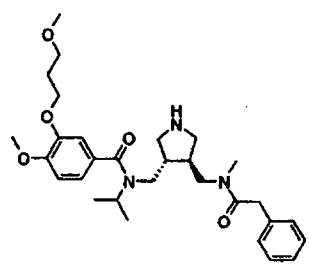
milimoles). La mezcla resultante se agita durante 1 hora, y el exceso de agente reductor se apaga con agua, se agrega CH_2Cl_2, y la mezcla de reacción se vierte en una solución acuosa saturada de $NaHCO_3$. La capa orgánica se separa, y la fase acuosa se extrae dos veces con CH_2Cl_2, se seca sobre Na_2SO_4, se filtra, y se concentra al vacío. El material crudo se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente: CH_2Cl_2/MeOH, de 100:0 a 95:5 + NH_4OH al 1 por ciento), para dar el producto del título. TLC, R_f (CH_2Cl_2/MeOH, 95:5) = 0.05. MS (LC-MS) $[M+H]^+$ = 508.1. t_R (HPLC, columna Nucleosil C18, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 4.53 minutos.

B. Terbutil-éster del ácido (3R*,4R*)-3-[(ciclopropan-carbonil-metil-amino)-metil]-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico.

A una solución del terbutil-éster del ácido (3R*,4R*)-3-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-4-metil-amino-metil-pirrolidin-1-carboxílico (134 miligramos, 0.264 milimoles) en CH_2Cl_2 (2 mililitros), se le agregan cloruro de ciclopropan-carbonilo (29 microlitros, 0.317 milimoles) y trietil-amina (44 microlitros, 0.317 milimoles) bajo una atmósfera de N_2. La mezcla se agita durante la noche a temperatura ambiente, se diluye con CH_2Cl_2, y se vierte en una solución acuosa saturada de

$NaHCO_3$. La capa orgánica se separa, y la acuosa se extrae dos veces con CH_2Cl_2. Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran, y se concentran. El producto crudo se utiliza en el siguiente paso sin purificación. TLC, R_f (CH_2Cl_2/ MeOH, 95:5) = 0.2. MS (LC-MS): 476.1 $[M+H-Boc]^+$; t_R (HPLC, columna Nucleosil C18, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.42 minutos.

Ejemplo 9:N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-N-{(3S,4S)-4-[(metil-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-benzamida



A una solución del terbutil-éster del ácido (3R,4R)-3-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-4-[(metil-fenil-acetil-amino)-metil]-pirrolidin-1-carboxílico (0.36 gramos, 0.575 milimoles) en 12 mililitros de CH_2Cl_2, se le agrega ácido trifluoroacético (0.664 mililitros, 8.62 milimoles). La mezcla se agita durante 2 horas a 30°C, y se vierte en una solución saturada de $NaHCO_3$. Las capas se separan, y la acuosa se retro-

extrae con CH_2Cl_2. Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran, y se concentran. A una solución de la base libre en dioxano (3 mililitros), se le agrega HCl 4N en dioxano (0.144 mililitros), y la solución resultante se liofiliza, para proporcionar la sal de clorhidrato correspondiente. TLC, R_f (CH_2Cl_2/MeOH, 95:5) = 0.1. MS (LC-MS): 526.1 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 4.41 minutos.

El material de inicio se prepara como sigue:

A. Terbutil-éster del ácido (3R,4R)-3-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-4-[(metil-fenil-acetil-amino)-metil]-pirrolidin-1-carboxílico.

El terbutil-éster del ácido (3R*,4R*)-3-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-4-[(metil-fenil-acetil-amino)-metil]-pirrolidin-1-carboxílico se separa en los enantiómeros individuales mediante HPLC quiral de preparación sobre una columna Chiralpak AD-H (4.6 x 250 milímetros, tamaño de partículas de 5 micras; velocidad de flujo de 1 mililitro/minuto, UV = 210 nanómetros, inyección = 1.7 gramos en 5 mililitros de etanol, y utilizando etanol como el eluyente, para dar el compuesto del título enantioméricamente puro: t_R (HPLC, Chiralpak AD-H,

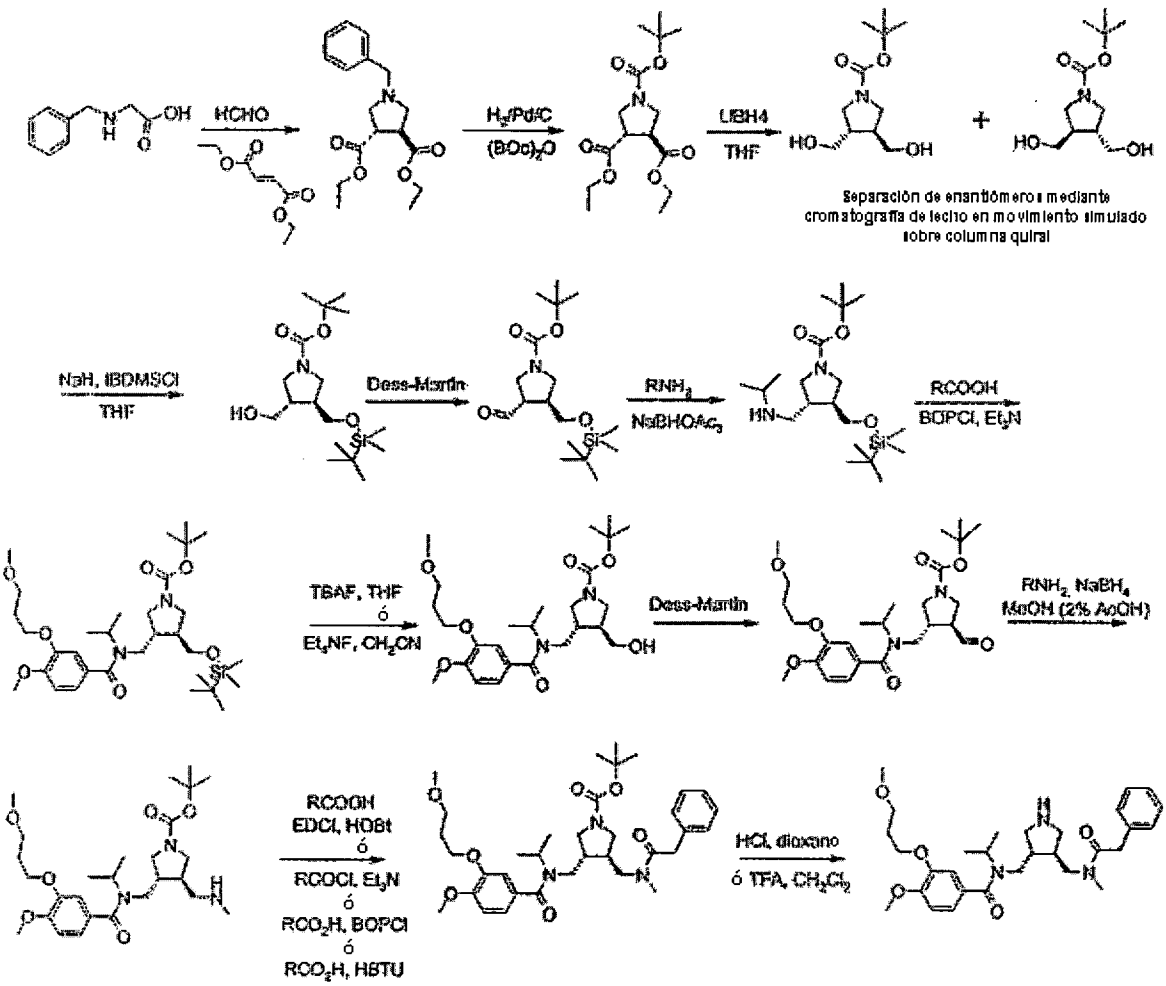
HPLC 250 x 4.6 milímetros, etanol, flujo: 0.5 mililitros/minuto): 26.46 minutos; y terbutil-éster del ácido (3S,4S)-3-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-4-[(metil-fenil-acetil-amino)-metil]-pirrolidin-1-carboxílico: t_R (HPLC, Chiralpak AD-H, HPLC 250 x 4.6 milímetros, etanol, flujo: 0.5 mililitros/minuto): 13.53 minutos.

B. Terbutil-éster del ácido (3R*,4R*)-3-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-4-metil-amino-metil-pirrolidin-1-carboxílico.

El compuesto del título se prepara a partir del terbutil-éster del ácido (3R*,4R*)-3-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-4-metil-amino-metil-pirrolidin-1-carboxílico (79 miligramos, 0.165 milimoles) y cloruro de fenil-acetilo, de acuerdo con el Ejemplo 8, paso de reacción B. R_f (CH_2Cl_2/MeOH, 95:5) = 0.4. MS (LC-MS): 526.1 $[M+H]^+$; t_R (Columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 4.71 minutos.

De una manera alternativa, el material de inicio de terbutil-éster del ácido (3R,4R)-3-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-4-[(metil-fenil-acetil-amino)-metil]-pirrolidin-1-carboxílico, se prepara de acuerdo con el Esquema de reacción 5 como sigue:

Esquema de reacción 5



A. Dietil-éster del ácido (3S*,4S*)-1-bencil-pirrolidin-3,4-dicarboxílico.

Una mezcla de N-bencil-glicina (51.3 gramos, 310.55 milimoles), fumarato de dietilo (51.85 mililitros, 316.76 milimoles), y polvo de para-formaldehído (10.25 gramos, 341.6 milimoles) en tolueno (500 mililitros), se calienta a reflujo durante 2 horas, mientras que se recolecta el agua utilizando un aparato Dean-Stark. El solvente se concentra, y la mezcla se purifica mediante

destilación al vacío (aproximadamente 50 mbar), destilándose el compuesto del título deseado a 80-85°C. TLC, R_f (CH_2Cl_2/acetona, 95:5) = 0.56. MS (LC-MS): 306.2 $[M+H]^+$; t_R (HPLC, columna RP8, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/2.5 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 4.35 minutos.

B. 3,4-dietil-éster de 1-terbutil-éster del ácido (3S*, 4S*)-pirrolidin-1,3,4-tricarboxílico.

Una mezcla de dietil-éster ácido (3S*,4S*)-1-bencil-pirrolidin-3,4-dicarboxílico (82.8 gramos, 271.14 milimoles), carbonato de diterbutilo (88.76 gramos, 406.71 milimoles), y Pd/C al 10 por ciento (8 gramos) en EtOH (1.5 mililitros), se agita bajo una atmósfera de hidrógeno. El material crudo se filtra sobre un cojín de Celite, y se concentra. El material crudo se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente: CH_2Cl_2/acetona, de 100:0 a 95:5). TLC, R_f (CH_2Cl_2/acetona, 95:5) = 0.51. MS (LC-MS): 216.2 $[M+H-Boc]^+$.

C. Terbutil-éster del ácido (3S*,4S*)-3,4-bis-hidroxi-metil-pirrolidin-1-carboxílico.

A una solución helada del 3,4-dietil-éster de 1-terbutil-éster del ácido (3S*,4S*)-pirrolidin-1,3,4-tri-carboxílico (36 gramos, 114.15 milimoles) en tetrahidrofurano (1 litro), se le agrega por goteo una solución de $LiBH_4$ (228.3 milimoles) en tetrahidrofurano (250 mililitros). La mezcla de reacción se agita durante la noche a

temperatura ambiente, y se apaga con una solución acuosa de NaOH 2H (400 mili-litros). Se agrega éter, las capas se separan, y la acuosa se retro-extrae dos veces con éter. Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran, y se concentran, para dar el compuesto del título, el cual se utiliza sin mayor purificación en el siguiente paso. TLC, R_f (CH_2Cl_2/MeOH, 95:5) = 0.14. MS (LC-MS): 232.2 $[M+H]^+$; t_R (HPLC, columna C18, del 5 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto): 3.37 minutos.

Terbutil-éster del ácido (3S,4S)-3,4-bis-hidroxi-metil-pirrolidin-1-carboxílico y terbutil-éster del ácido (3R,4R)-3,4-bis-hidroxi-metil-pirrolidin-1-carboxílico.

Los dos enantiómeros se separan mediante HPLC de preparación quiral, utilizando cromatografía de lecho en movimiento simulado (SMB) Tecnología "UOP SORBEX Prep." con 16 columnas "Princeton Chromatography Inc." (7.5 x 2.12 centímetros), fase estacionaria: Chiralpak AD Prep. 20 µM (eluyente: hexano/EtOH/MeOH, 90:5:5).

Terbutil-éster del ácido (3S,4S)-3,4-bis-hidroxi-metil-pirrolidin-1-carboxílico: t_R (Chiralpak AD-H, 250 x 4.6 milímetros, velocidad de flujo de 1 mililitro/minuto) (eluyente: hexano/EtOH, 90:10): 6.4 minutos $[\alpha]_D$ = -11.1 (c = 1.795, $CHCl_3$).

Terbutil-éster del ácido (3R,4R)-3,4-bis-hidroxi-metil-pirrolidin-1-carboxílico: t_R (Chiralpak AD-H, 250 x 4.6 milímetros,

velocidad de flujo de 1 mililitro/minuto) (eluyente: hexano/EtOH, 90:10): 8.58 minutos $[\alpha]_D$ = +10.2 (c = 1.795, $CHCl_3$).

D. Terbutil-éster del ácido (3S,4S)-3-(terbutil-di-metil-silaniloxi-metil)-4-hidroxi-metil-pirrolidin-1- carboxílico.

A una suspensión de hidruro de sodio (al 60 por ciento en aceite, 0.996 gramos, 24.9 milimoles) (previamente lavado con pentano) en tetrahidrofurano (40 mililitros), se le agrega por goteo, bajo una atmósfera de nitrógeno, una solución de terbutil-éster del ácido (3S,4S)-3,4-bis-hidroxi-metil-pirrolidin-1-carboxílico (4.8 gramos, 20.75 milimoles) en tetrahidrofurano (40 mililitros) a 0°C. La mezcla se agita durante 1.5 horas a 0°C antes de la adición por goteo de una solución de terbutil-(cloro)-dimetil-silano (3.44 gramos, 22.83 milimoles) en tetrahidrofurano (40 mililitros). La mezcla resultante se agita adicionalmente durante 1 hora a temperatura ambiente, luego se vierte en una solución acuosa de $NaHCO_3$ (5 por ciento) (150 mililitros), y se extrae 3 veces con Et_2O. Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran, y se concentran. El material crudo se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente: CH_2Cl_2/MeOH, de 99:1 a 93:7). TLC, R_f (CH_2Cl_2/MeOH, 95:5) = 0.33. MS (LC-MS): 346.2 $[M+H]^+$.

E. Terbutil-éster del ácido (3S,4S)-3-(terbutil-di-metil-silaniloxi-metil)-4-formil-pirrolidin-1-carboxílico.

A una mezcla bien agitada del terbutil-éster del ácido (3S,4S)-3-(terbutil-dimetil-silaniloxi-metil)-4-hidroxi-metil-

pirrolidin-1-carboxílico (8.2 gramos, 23.73 milimoles) y peryodinano de Dess-Martin (10.06 gramos, 23.73 milimoles) en CH_2Cl_2 (60 mililitros), se le agrega lentamente CH_2Cl_2 húmedo (0.47 mililitros de agua en 60 mililitros de CH_2Cl_2). La solución transparente se hace nebulosa hacia el final de la adición de CH_2Cl_2 húmedo, y se agita adicionalmente durante la noche. Entonces se concentra hasta unos cuantos mililitros de solvente mediante evaporación giratoria, y se recupera en Et_2O. Se agrega una solución de 1:1 de $Na_2S_2O_3$ al 10 por ciento/$NaHCO_3$ acuoso saturado. Las capas se separan, y el extracto orgánico se lava sucesivamente con H_2O y salmuera. Los lavados acuosos se retro-extraen con Et_2O, y esta capa orgánica se lava con H_2O y salmuera. Las capas orgánicas combinadas se secan con Na_2SO_4, se filtran, y se concentran. La mezcla cruda se utiliza en el siguiente paso sin mayor purificación. TLC, R_f (CH_2Cl_2/MeOH, 95:5) = 0.42. MS (LC-MS): 244.2 $[M+H-Boc]^+$; t_R (HPLC, columna C18, del 5 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto): 6.45 minutos.

F. Terbutil-éster del ácido (3S,4R)-3-(terbutil-di-metil-silaniloxi-metil)-4-(isopropil-amino-metil)-pirrolidin-1-carboxílico.

Una solución del terbutil-éster del ácido (3S,4S)-3-(terbutil-dimetil-silaniloxi-metil)-4-formil-pirrolidin-1-carboxílico (7.7

gramos, 22.41 milimoles) e isopropil-amina (5.78 mililitros, 67.24 milimoles) en 1,2-dicloro-etano (200 mililitros), se agita durante 25 minutos antes de la adición de $NaBH(OAc)_3$ (11.88 gramos, 56.03 milimoles). La solución se agita durante 5 horas, luego se diluye con CH_2Cl_2, y se lava con una solución acuosa saturada de $NaHCO_3$. La capa acuosa se retro-extrae dos veces con CH_2Cl_2, y los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran, y se concentran. El material crudo se utiliza en el siguiente paso sin mayor purificación. TLC, R_f (CH_2Cl_2/MeOH, 9:1) = 0.39. MS (LC-MS): 387.2 $[M+H]^+$.

G. Terbutil-éster del ácido (3S,4R)-3-(terbutil-di-metil-silaniloxi-metil)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico.

Una mezcla del terbutil-éster del ácido ((3S,4R)-3-(terbutil-dimetil-silaniloxi-metil)-4-(isopropil-amino-metil)-pirrolidin-1-carboxílico (8.9 gramos, 23.02 milimoles), ácido 3-(3-metoxi-propoxi)-4-metoxi-benzoico (6.08 gramos, 25.32 milimoles), cloruro de bis-(2-oxo-3-oxazolidinil)-fosfínico (6.45 gramos, 25.32 milimoles), y trietil-amina (7.62 mili-litros, 92.07 milimoles) en CH_2Cl_2 (230 mililitros), se pone a reflujo durante 3 horas. La reacción se apaga mediante la adición de una solución acuosa saturada de $NaHCO_3$. La capa orgánica se separa, y la fase acuosa se extrae 3 veces con AcOEt. Los extractos orgánicos combinados se secan (Na_2SO_4), y el solvente se retira al vacío. El producto crudo se purifica mediante cromatografía por evaporación

instantánea sobre gel de sílice (eluyente: CH_2Cl_2/acetona, 95:5, hasta CH_2Cl_2/MeOH, 95:5), para dar el producto del título. TLC, R_f (CH_2Cl_2/MeOH, 95:5) = 0.47. MS (LC-MS): 609.4 $[M+H]^+$; t_R (HPLC, columna C18, del 5 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto): 7.05 minutos.

H. Terbutil-éster del ácido (3S,4R)-3-hidroxi-metil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico.

A una solución del terbutil-éster del ácido (3S,4R)-3-(terbutil-dimetil-silaniloxi-metil)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (8.75 gramos, 14.37 milimoles) en tetrahidro-furano (40 mililitros), se le agrega trihidrato de fluoruro de tetrabutil-amonio (6.8 gramos, 24.55 milimoles), bajo una atmósfera de nitrógeno. La mezcla de reacción se agita durante la noche. Se agregan agua y AcOEt, las capas se separan, y la acuosa se extrae dos veces con AcOEt. Los extractos orgánicos combinados se secan (Na_2SO_4), y el solvente se retira al vacío. El producto crudo se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente: CH_2Cl_2/MeOH, de 97:3 a 95:5), para dar el producto del título. TLC, R_f (CH_2Cl_2/MeOH, 95:5) = 0.3. MS (LC-MS): 395.1 $[M+H\text{-Boc}]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5

minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.01 minutos.

I. Terbutil-éster del ácido (3S,4R)-3-formil-4-({iso-propil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico.

El compuesto del título se prepara de una manera análoga a la descrita para el compuesto del título de E en el Esquema de reacción 5, a partir del terbutil-éster del ácido (3S,4R)-3-hidroxi-metil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico.TLC, R_f CH_2Cl_2/ MeOH, 95:5) = 0.3. t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.16 minutos.

J. Terbutil-éster del ácido (3R,4R)-3-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-4-metil-amino-metil-pirrolidin-1-carboxílico.

A una solución del terbutil-éster del ácido (3S,4R)-3-formil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (2.7 gramos, 5.48 mili-moles) en MeOH (conteniendo AcOH al 2 por ciento, 25 mili-litros), se le agrega metil-amina (13.7 mililitros, 27.41 mili-moles, 2M en MeOH). La solución se agita a temperatura ambiente durante 1 hora bajo una atmósfera de nitrógeno, y se enfría a 10°C, antes de la adición

cuidadosa de $NaBH_4$ (0.415 gramos, 10.96 milimoles) (¡exotérmico!). La mezcla resultante se deja llegar a la temperatura ambiente, y se agita durante 1.5 horas. El exceso de agente reductor se apaga con agua, se agrega AcOEt, y la mezcla de reacción se vierte en una solución acuosa saturada de $NaHCO_3$. La capa orgánica se separa, y la capa acuosa se extrae dos veces con AcOEt, se seca sobre Na_2SO_4, se filtra, y se concentra al vacío. El material crudo se utiliza en el siguiente paso sin mayor purificación. TLC, R_f (CH_2Cl_2/MeOH, 95:5) = 0.05. MS (LC-MS) $[M+H]^+$ = 508.1. t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 4.53 minutos.

K. Terbutil-éster del ácido (3R,4R)-3-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-4-[(metil-fenil-acetil-amino)-metil]-pirrolidin-1-carboxílico.

A una solución del terbutil-éster del ácido (3R,4R)-3-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-4-metil-amino-metil-pirrolidin-1-carboxílico (2 gramos, 3.35 milimoles) en CH_2Cl_2 (25 mililitros), se le agregan cloruro de fenil-acetilo (0.53 mililitros, 4.02 milimoles) y trietil-amina (0.56 mililitros, 4.02 milimoles) bajo una atmósfera de N_2 a 0°C. La mezcla se agita durante 30 minutos a 0°C, luego se deja llegar a la temperatura ambiente, y se agita adicionalmente durante 1 hora.

La mezcla de reacción se diluye con CH_2Cl_2, y se vierte en una solución acuosa saturada de $NaHCO_3$. La capa orgánica se separa, y la acuosa se extrae dos veces con CH_2Cl_2. Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran, y se concentran. El producto crudo se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (ciclo-hexano/AcOEt, de 20:80 a 0:100), para dar el compuesto del título. TLC, R_f (CH_2Cl_2/MeOH, 95:5) = 0.4. MS (LC-MS): 526 $[M\text{-}Boc+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.71 minutos.

De una forma similar a la descrita anteriormente para el Ejemplo 9/paso de reacción J, se prepara el

terbutil-éster del ácido (3R*,4R*)-3-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-4-metil-amino-metil-pirrolidin-1-carboxílico

a partir del terbutil-éster del ácido (3S*,4R*)-3-formil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico, mediante aminación reductiva con metil-amina, en la presencia de $NaBH_4$: TLC, R_f (CH_2Cl_2/ MeOH, 95:5) = 0.05. MS (LC-MS) $[M+H]^+$ = 508.1. t_R (HPLC, columna Nucleosil C18, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético

al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 4.53 minutos.

A. Terbutil-éster del ácido (3S*,4S*)-3-(terbutil-di-metil-silaniloxi-metil)-4-hidroxi-metil-pirrolidin-1-carboxílico.

El compuesto del título se prepara de una manera similar a la descrita para el Ejemplo 9/paso de reacción D, a partir del terbutil-éster del ácido (3S*,4S*)-3,4-bis-hidroxi-metil-pirrolidin-1-carboxílico (25.0 gramos, 108 milimoles), terbutil-(cloro)-dimetil-silano (17.9 gramos, 119 milimoles), y NaH (3.11 gramos, 130 milimoles; dispersión al 55-65 por ciento en aceite) en tetrahidrofurano (0.6 litros), como un aceite amarillento. MS: 346.2 $[M+H]^+$.

B. Terbutil-éster del ácido (3S*,4S*)-3-(terbutil-di-metil-silaniloxi-metil)-4-formil-pirrolidin-1-carboxílico.

El compuesto del título se prepara de una manera similar a la descrita para el Ejemplo 9/paso de reacción E, a partir del terbutil-éster del ácido (3S*,4S*)-3-(terbutil-di-metil-silaniloxi-metil)-4-hidroxi-metil-pirrolidin-1-carboxílico (10.4 gramos, 58.9 milimoles) y peryodinano de Dess-Martin (25.0 gramos, 58.9 milimoles) en CH_2Cl_2 (150 mililitros), CH_2Cl_2 lentamente humedecido (1.17 mililitros de agua en 150 mililitros de CH_2Cl_2), como un aceite incoloro. MS: 244.2 $[M+H-Boc]^+$. t_R (HPLC, columna C18, del 5 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto): 6.46 minutos.

C. Terbutil-éster del ácido (3S*,4R*)-3-(terbutil-di-metil-silaniloxi-metil)-4-(isopropil-amino-metil)-pirrolidin-1-carboxílico.

El compuesto del título se prepara de una manera similar a la descrita para el Ejemplo 9/paso de reacción F, a partir del terbutil-éster del ácido (3S*,4S*)-3-(terbutil-di-metil-silaniloxi-metil)-4-formil-pirrolidin-1-carboxílico (19.3 gramos, 56.1 milimoles), isopropil-amina (14.5 mililitros, 168 milimoles), y $NaBH(OAc)_3$ (29.7 gramos, 140 milimoles) en 1,2-dicloro-etano (0.5 litros), como un aceite amarillento. MS: 387.2 $[M+H]^+$. t_R (HPLC, columna C18, del 5 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto): 5.34 minutos.

D. Terbutil-éster del ácido (3S*,4R*)-3-(terbutil-di-metil-silaniloxi-metil)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico.

El compuesto del título se prepara de una manera similar a la descrita para el Ejemplo 9/paso de reacción G, a partir del terbutil-éster del ácido ((3S*,4R*)-3-(terbutil-di-metil-silaniloxi-metil)-4-(isopropil-amino-metil)-pirrolidin-1-carboxílico (22.9 gramos, 59.1 milimoles), ácido 3-(3-metoxi-propoxi)-4-metoxi-benzoico (15.6 gramos, 65.1 milimoles), cloruro bis-(2-oxo-3-oxazolidinil)-fosfínico (16.6 gramos, 65.1 milimoles) y trietil-amina (19.6 mililitros, 237 milimoles) en CH_2Cl_2 (0.6 litros) como un

aceite amarillento. MS: 609.4 $[M+H]^+$; t_R (HPLC, columna C18, del 5 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto): 7.06 minutos.

E. Terbutil-éster del ácido (3S*,4R*)-3-hidroxi-metil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico.

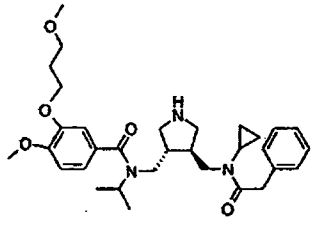
El compuesto del título se prepara de una manera similar a la descrita en el Ejemplo 9/paso de reacción H, a partir del terbutil-éster del ácido (3S*,4R*)-3-(terbutil-di-metil-silaniloxi-metil)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (25.0 gramos, 41.1 milimoles) y trihidrato de fluoruro de tetrabutil-amonio (19.4 gramos, 61.6 milimoles) en tetrahidrofurano (150 mililitros) como un aceite incoloro. MS: 495.2 $[M+H]^+$; t_R (HPLC, columna C18, del 5 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/1.5 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 4.84 minutos.

F. Terbutil-éster del ácido (3S*,4R*)-3-formil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico.

El compuesto del título se prepara de una manera similar a la descrita para el Ejemplo 9/paso de reacción I, a partir del terbutil-éster del ácido (3S*,4R*)-3-hidroxi-metil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-

carboxílico (4.9 gramos, 9.95 milimoles) y peryodinano de Dess-Martin (4.22 gramos, 9.95 milimoles) en CH_2Cl_2 (30 mililitros), y CH_2Cl_2 lentamente humedecido (0.20 mililitros de agua en 30 mililitros de CH_2Cl_2), como un aceite incoloro. MS: 437.2 $[M+H-BOC]^+$. t_R (HPLC, columna Nucleosil C18, del 5 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/1.5 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 4.99 minutos.

Ejemplo 10: N-{(3S,4S)-4-[(ciclopropil-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida



Una solución del terbutil-éster del ácido (3R,4R)-3-[(ciclopropil-fenil-acetil-amino)-metil]-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (0.32 gramos, 0.48 milimoles) en una solución de HCl 4N en dioxano (2.0 mililitros), se agita a temperatura ambiente durante la noche. Entonces la mezcla de reacción se seca por congelación para proporcionar la sal de clorhidrato correspondiente como un sólido blanco. MS: 552.2 $[M]^+$; t_R (HPLC, columna Nucleosil C18HD, del 5 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por

ciento de CH_3CN/1.5 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto): 4.72 minutos.

El material de inicio se prepara como sigue:

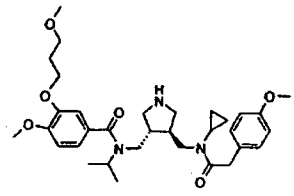
A. Terbutil-éster del ácido (3R,4R)-3-(ciclopropil-amino-metil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico.

Una solución del terbutil-éster del ácido (3S,4R)-3-formil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (7.45 gramos, 15.1 mili-moles; Ejemplo 9/paso de reacción I) y ciclopropil-amina (5.30 mililitros, 75.6 milimoles) en MeOH (conteniendo AcOH al 2 por ciento, 90 mililitros), se agita durante 1 hora a temperatura ambiente, seguido por la adición en porciones de $NaBH_4$ (1.14 gramos, 30.2 milimoles). Después de agitar durante 1 hora, la mezcla de reacción se concentra hasta una tercera parte de su volumen, se agregan agua y una solución saturada de $NaHCO_3$, y la capa acuosa se extrae con AcOEt. Los orgánicos combinados se secan (Na_2SO_4) y se evaporan a sequedad, para proporcionar el compuesto del título como un aceite incoloro. El material crudo se utiliza en el siguiente paso sin purificación. MS (LC-MS): $[M+H]^+$ = 534.2. t_R (HPLC, columna Nucleosil C18HD, del 5 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/1.5 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto): 4.79 minutos.

B. Terbutil-éster del ácido (3R,4R)-3-[(ciclopropil-fenil-acetil-amino)-metil]-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico.

A una solución del terbutil-éster del ácido (3R,4R)-3-ciclopropil-amino-metil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (0.30 gramos, 0.56 milimoles) en CH_2Cl_2 (6 mililitros), se le agregan subsecuentemente Et_3N (0.094 mililitros, 0.67 mili-moles), hidrato de 1-hidroxi-benzotriazol (0.09 gramos, 0.67 milimoles), clorhidrato de N-(3-dimetil-amino-propil)-N'-etil-carbodi-imida (0.129 gramos, 0.67 milimoles), y ácido fenil-acético (0.09 gramos, 0.67 milimoles), seguido por agitación durante la noche. La mezcla de reacción se diluye con CH_2Cl_2, y luego se lava con HCl 1N (5 mililitros), $NaHCO_3$ acuoso saturado, y salmuera; la capa orgánica se seca sobre $MgSO_4$ y se concentra. La purificación mediante cromatografía por evaporación instantánea (eluyente: hexano/ AcOEt, 25:75, luego AcOEt al 100 por ciento), da el compuesto del título como un aceite incoloro. MS (LC-MS): 652.4 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18HD, del 5 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/1.5 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto): 5.80 minutos.

Ejemplo 11: N-[(3S*,4S*)-4-({ciclopropil-[2-(4-metoxi-fenil)-acetil]-amino}-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida



A una solución del terbutil-éster del ácido (3R*,4R*)-3-({ciclopropil-[2-(4-metoxi-fenil)-acetil]-amino}-metil)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (0.17 gramos, 0.26 mili-moles) en dioxano (1 mililitro), se le agrega HCl 4N en dioxano (0.647 mililitros), y la solución resultante se liofiliza para proporcionar la sal de clorhidrato correspondiente. TLC, R_f (CH_2Cl_2/MeOH, 9:1 + NH_4OH al 10 por ciento) = 0.2. MS (LC-MS): 582.4 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 5 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto): 4.06 minutos.

El material de inicio se prepara como sigue:

A. Terbutil-éster del ácido (3R*,4R*)-3-ciclopropil-amino-metil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico.

El compuesto del título se prepara de una manera análoga a la descrita para el compuesto del título de J en el Ejemplo 9, a partir del terbutil-éster del ácido (3S*,4R*)-3-formil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico y ciclopropil-amina. TLC, R_f (CH_2Cl_2/MeOH, 9:1 + NH_4OH al 10 por ciento) = 0.48. MS (LC-MS): 534.4 $[M+H]^+$; t_R

(HPLC, columna Nucleosil C18 de Macherey-Nagel, del 5 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto): 4.53 minutos.

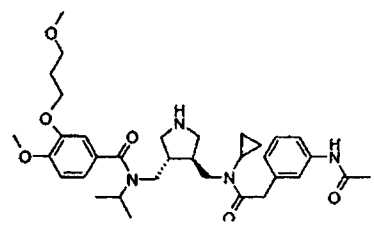
B. Terbutil-éster del ácido (3R*,4R*)-3-({ciclopropil-[2-(4-metoxi-fenil)-acetil]-amino}-metil)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico.

A una solución de ácido 4-metoxi-fenil-acético (0.075 gramos, 0.45 milimoles) en CH_2Cl_2 (3 mililitros), se le agregan trietil-amina (0.063 mililitros, 0.45 milimoles), hidrato de 1-hidroxi-benzotriazol (0.061 gramos, 0.45 milimoles), y clorhidrato de N-(3-dimetil-amino-propil)-N'-etil-carbodi-imida (EDC) (0.086 gramos, 0.45 milimoles), seguido por terbutil-éster del ácido (3R*,4R*)-3-ciclopropil-amino-metil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (0.2 gramos, 0.375 mili-moles). La mezcla resultante se agita durante 2 días a temperatura ambiente, luego se diluye con CH_2Cl_2, y se vierte en una solución acuosa saturada de $NaHCO_3$. La capa orgánica se separa, y la acuosa se extrae dos veces con CH_2Cl_2. Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran, y se concentran. El producto crudo se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente: ciclo-hexano/AcOEt, de 50:50 a 0:100), para dar el compuesto del título. TLC, R_f (CH_2Cl_2/ MeOH, 95:5) = 0.35. MS (LC-MS): 682.4 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18 de

Macherey-Nagel, del 5 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto): 5.77 minutos.

De una manera alternativa, la reacción de acoplamiento se lleva a cabo de una manera similar a la descrita anteriormente utilizando 1.1 equivalentes de HOBt, EDC, NEt_3, y una mezcla de dimetil-formamida/tetrahidro-furano, 1:1.

Ejemplo 12: N-[(3S*,4S*)-4-({[2-(3-acetil-amino-fenil)-acetil]-ciclopropil-amino}-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida



A una solución del terbutil-éster del ácido (3R*,4R*)-3-({[2-(3-acetil-amino-fenil)-acetil]-ciclopropil-amino}-metil)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (0.31 gramos, 0.44 milimoles) en dioxano (15 mililitros), se le agrega HCl 4N en dioxano (6 mililitros), la solución resultante se agita a temperatura ambiente durante 8 horas, y luego se liofiliza para proporcionar la sal de clorhidrato correspondiente. MS (LC-MS): 609.1 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.03 minutos.

El material de inicio se prepara como sigue:

A. Terbutil-éster del ácido (3R*,4R*)-3-({ciclopropil-[2-(3-nitro-fenil)-acetil]-amino}-metil)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico.

A 0°C, se agrega HBTU (426 miligramos, 1.12 mili-moles) a una solución de ácido 3-nitro-fenil-acético (187 mili-gramos, 1.03 milimoles) en CH_3CN (10 mililitros), y la solución resultante se agita durante 10 minutos. Luego se agrega una solución del terbutil-éster del ácido (3R*,4R*)-3-ciclopropil-amino-metil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (0.2 gramos, 0.375 milimoles), y trietil-amina (1.04 mililitros, 7.5 milimoles) en CH_3CN (10 mililitros) a 0°C, y la mezcla de reacción se agita a temperatura ambiente durante otras 3 horas. Para el procesamiento, se agrega una solución saturada de $NaHCO_3$, y la mezcla se extrae con acetato de etilo. El lavado de los extractos combinados con salmuera, el secado (Na_2SO_4), la filtración, y la evaporación del solvente, proporcionan el producto crudo, el cual se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente: CH_2Cl_2 hasta CH_2Cl_2/MeOH, 9:1), para dar el compuesto del título. MS (LC-MS): 597.0 $[M+H-Boc]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 6.47 minutos.

B. Terbutil-éster del ácido (3R*,4R*)-3-({[2-(3-amino-fenil)-acetil]-ciclopropil-amino}-metil)-4-({iso-propil-[4-metoxi-3-(3-metoxi-

propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico.

A temperatura ambiente, se pasa H_2 a través de una suspensión de terbutil-éster del ácido (3R*,4R*)-3-({ciclopropil-[2-(3-nitro-fenil)-acetil]-amino}-metil)-4-({iso-propil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (660 miligramos, 0.95 milimoles) y Níquel de Raney (100 miligramos) durante varias horas. Después de terminarse la reacción, la mezcla se filtra sobre Celite, y el solvente se evapora, para dar el compuesto del título, el cual se utiliza sin mayor purificación. MS (LC-MS): 667.0 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.33 minutos.

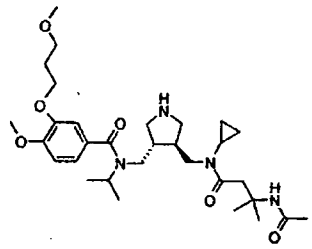
C. Terbutil-éster del ácido (3R*,4R*)-3-({[2-(3-acetil-amino-fenil)-acetil]-ciclopropil-amino}-metil)-4-({iso-propil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico.

Se agregan trietil-amina (67 microlitros, 0.48 mili-moles), DMAP (0.4 miligramos, 0.003 milimoles), y anhídrido acético (46 microlitros, 0.48 milimoles), a una solución de terbutil-éster del ácido (3R*,4R*)-3-({[2-(3-amino-fenil)-acetil]-ciclopropil-amino}-metil)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (215 miligramos, 0.32 milimoles) en tetrahidrofurano (20 mili-litros). La mezcla de reacción se agita a temperatura ambiente durante 16 horas, antes de agregar agua para el procesamiento. La extracción con acetato de etilo, el secado de los extractos combinados (Na_2SO_4), la

filtración, y la evaporación del solvente, proporcionan el producto crudo, el cual se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente: CH_2Cl_2 hasta CH_2Cl_2/MeOH, 9:1), para dar el compuesto del título. MS (LC-MS): 709.1 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 6.04 minutos.

En el siguiente ejemplo se describe un método alternativo para la reacción de desprotección de N-Boc:

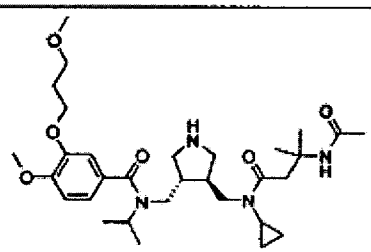
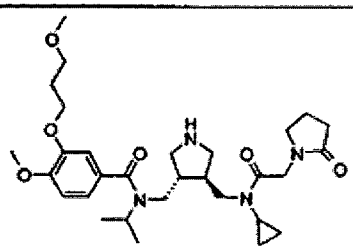
Ejemplo 13: N-((3S,4S)-4-{[(3-acetil-amino-3-metil-butiril)-ciclopropil-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida

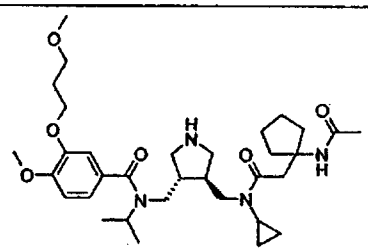
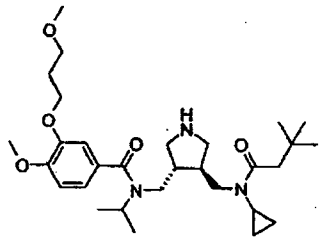
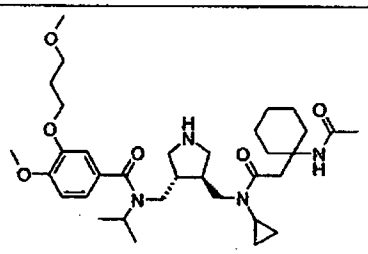
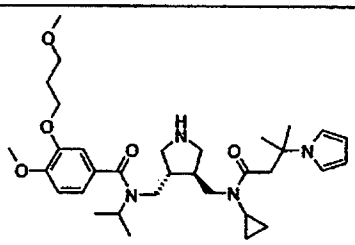
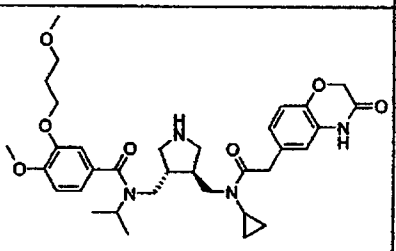
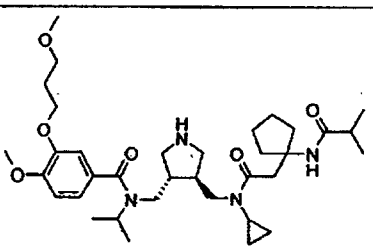


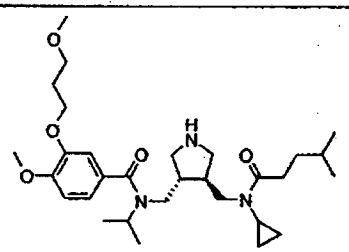
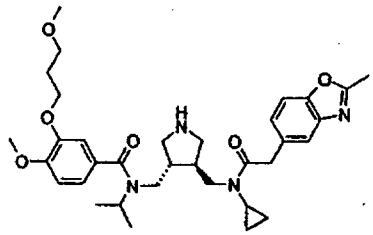
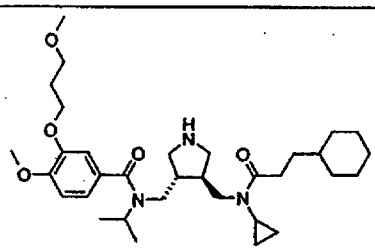
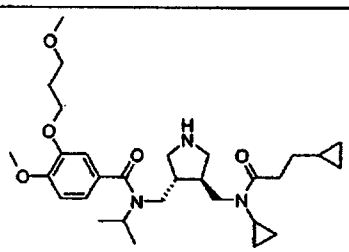
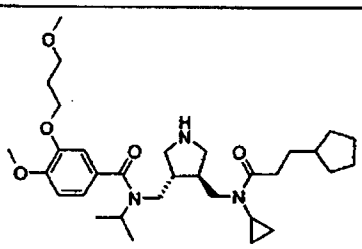
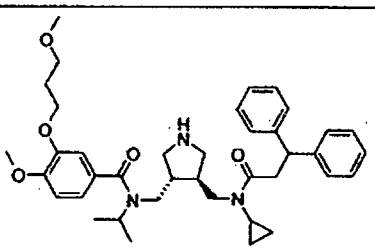
Se agrega $ZnBr_2$ (110 miligramos, 0.49 milimoles) a una solución de terbutil-éster del ácido (3R,4R)-3-{[(3-acetil-amino-3-metil-butiril)-ciclopropil-amino]-metil}-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (150 miligramos, 0.22 milimoles) en 1,2-dicloro-etano (5 mililitros), y la suspensión resultante se agita a 55°C durante 16 horas. Con el objeto de impulsar la reacción hasta terminar, se agrega otra porción de $ZnBr_2$ (50 miligramos, 0.22 milimoles), y se continúa el calentamiento durante otras 24 horas. Para

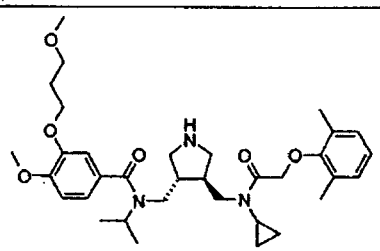
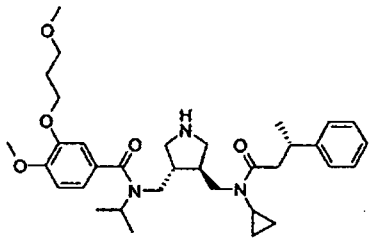
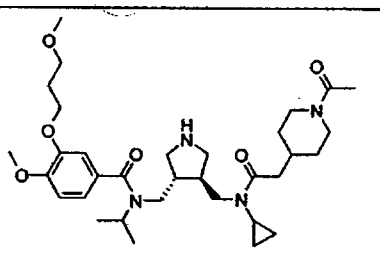
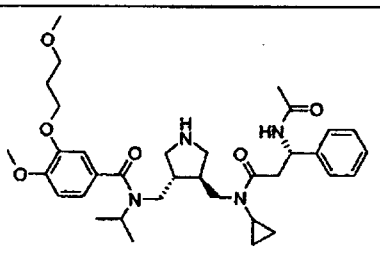
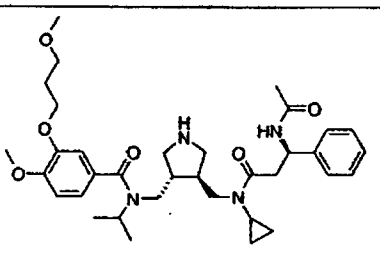
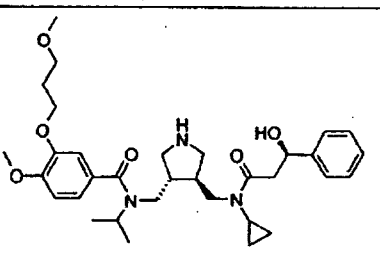
el procesamiento, se agrega una solución saturada de $NaHCO_3$, y la mezcla se extrae con CH_2Cl_2. El secado (Na_2SO_4) de los extractos combinados, la filtración, y la evaporación del solvente, proporcionan el producto deseado como la base libre. La base libre se disuelve en dioxano (2 mililitros), y se agrega ácido fumárico (11 miligramos, 0.11 milimoles). La liofilización produce el compuesto del título como la sal de hemifumarato. MS (LC-MS): 575.0 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 4.90 minutos.

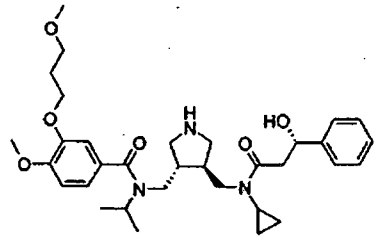
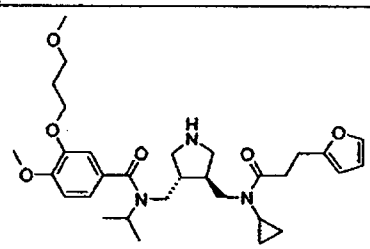
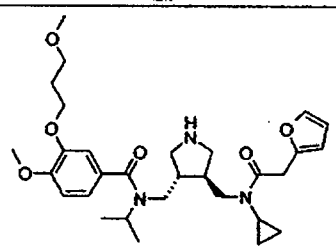
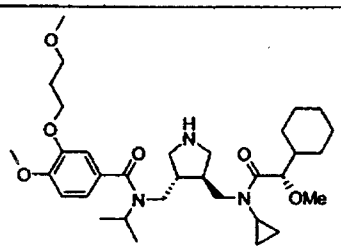
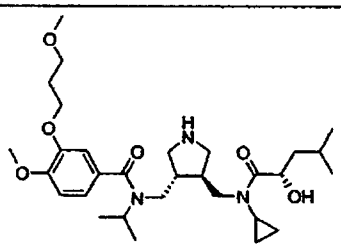
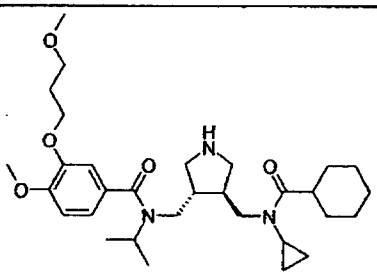
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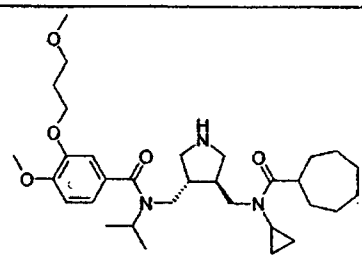
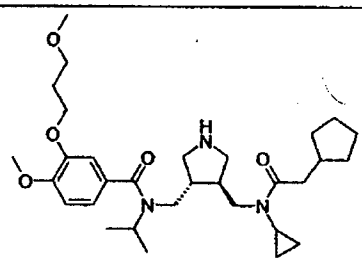
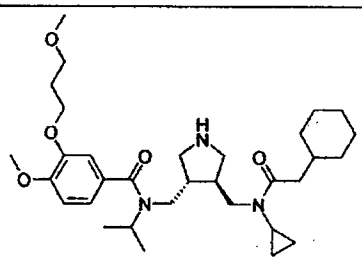
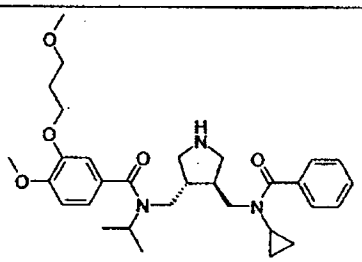
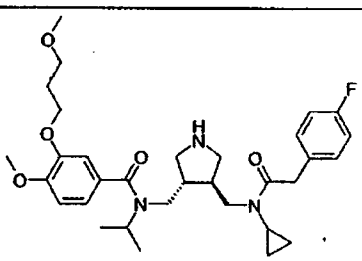
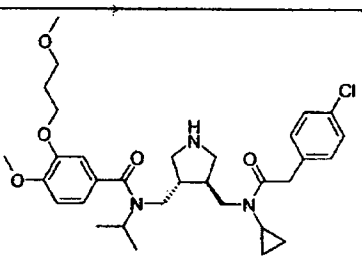
Ejemplo	Configuración	Estructura	$[M+H]^+$	t_R (HPLC)
14	(3S*, 4S*)		575.1	4.18[a]
15	(3S*, 4S*)		559.1	4.04[a]

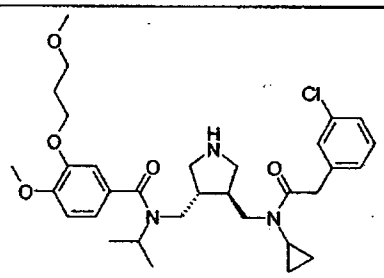
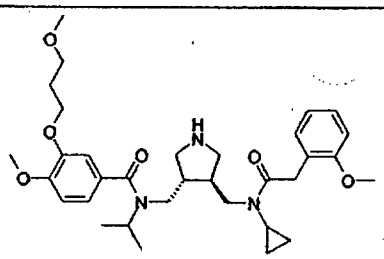
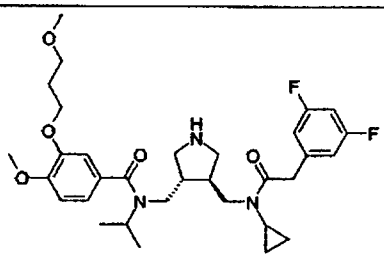
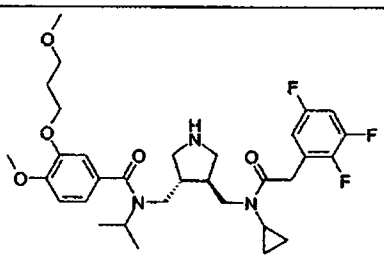
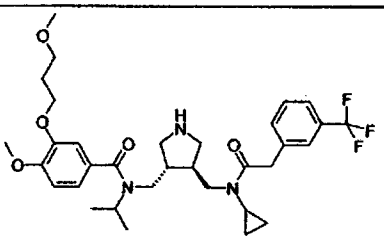
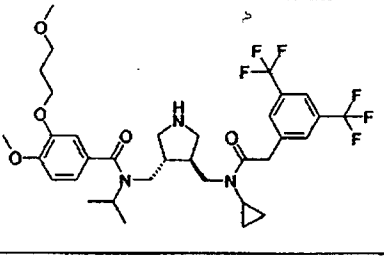
16	(3S*, 4S*)		601.2	4.34[a]
17	(3S*, 4S*)		532.1	4.72[a]
18	(3S*, 4S*)		615.2	4.52[a]
19	(3S*, 4S*)		583.3	4.82[a]
20	(3S*, 4S*)		623.4	4.49[a]
21	(3S*, 4S*)		629.7	4.80[a]

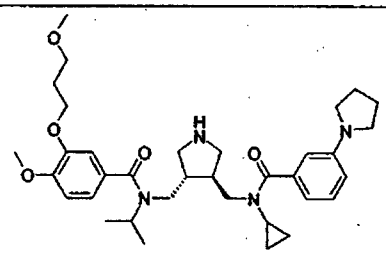
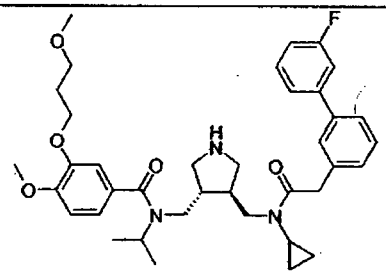
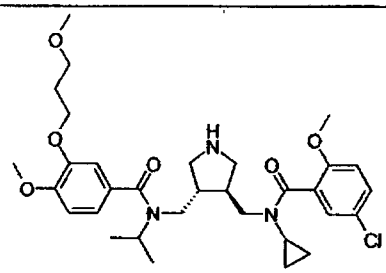
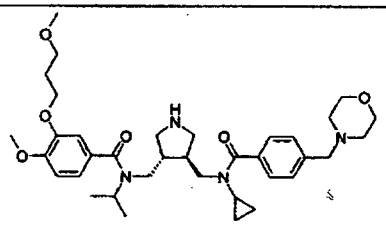
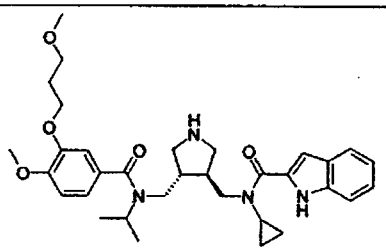
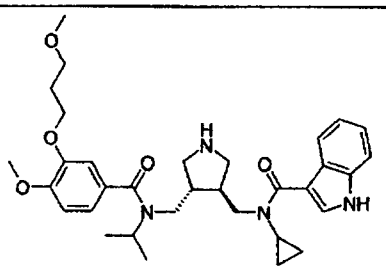
22	(3S*, 4S*)		532.3	5.12[a]
23	(3S*, 4S*)		607.2	5.19[a]
24	(3S*, 4S*)		572.3	5.99[a]
25	(3S, 4S)		530.2	5.87[a]
26	(3S, 4S)		558.3	6.19[a]
27	(3S, 4S)		642.3	5.51[a]

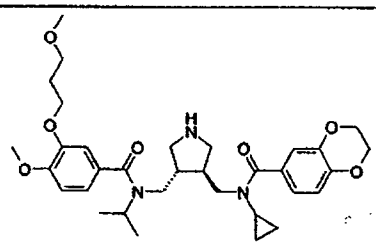
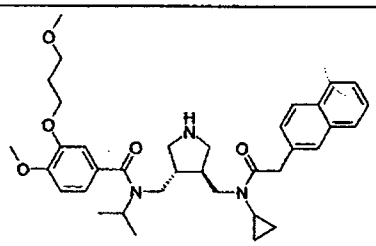
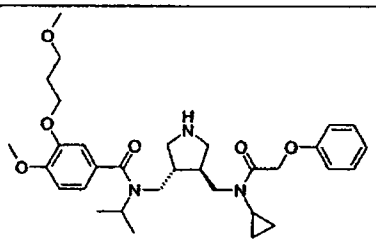
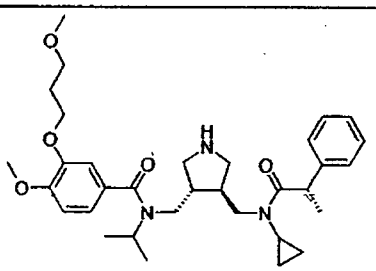
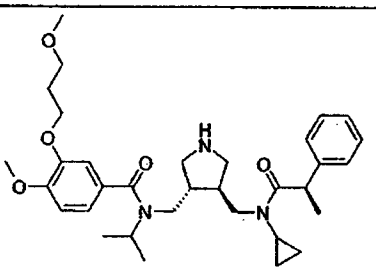
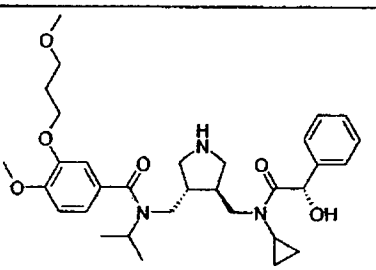
28	(3S, 4S)		596.3	5.44[a]
29	(3S, 4S)		580.0	4.95[a]
30	(3S, 4S)		601.5	3.04[b]
31	(3S, 4S)		623.5	0.36[b]
32	(3S, 4S)		623.5	0.35[b]
33	(3S, 4S)		582.2	4.46[a]

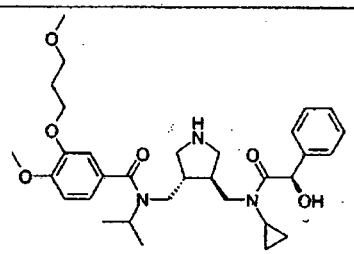
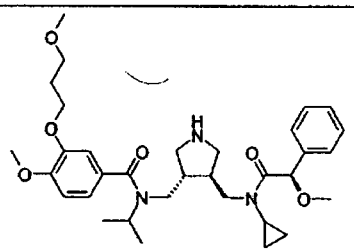
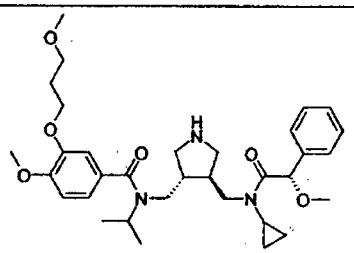
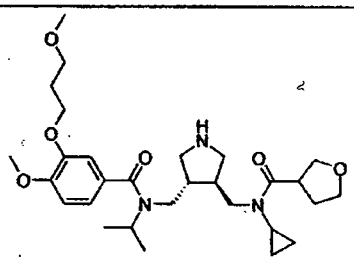
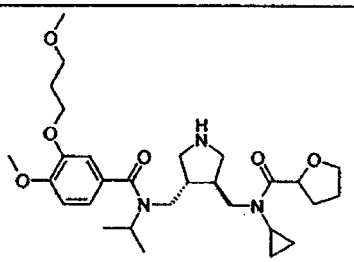
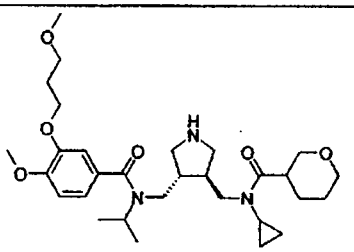
34	(3S, 4S)		582.2	4.50[a]
35	(3S, 4S)		556.3	4.67[a]
36	(3S, 4S)		542.2	4.48[a]
37	(3S, 4S)		588.3	2.89[c]
38	(3S, 4S)		548.2	2.41[d]
39	(3S*, 4S*)		544.4	4.69[e]

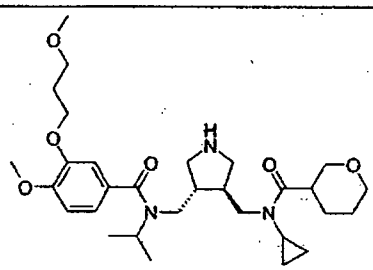
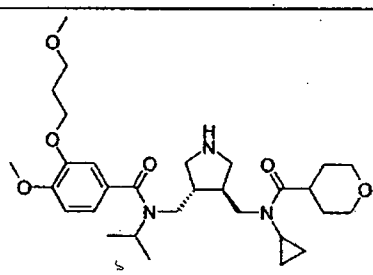
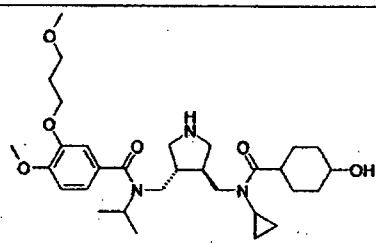
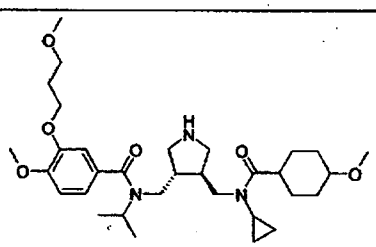
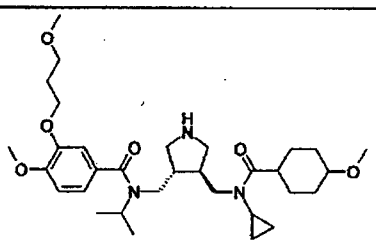
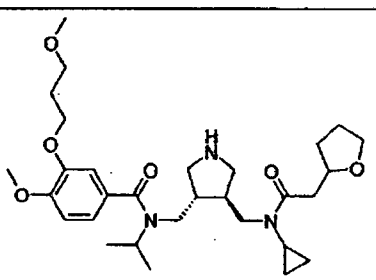
40	(3S,4S)		558.2	4.48[f]
41	(3S,4S)		544.3	4.97[e]
42	(3S*, 4S*)		558.4	5.28[e]
43	(3S*, 4S*)		538.2	4.61[e]
44	(3S*, 4S*)		570.2	4.85[e]
45	(3S,4S)		586.2	5.04[e]

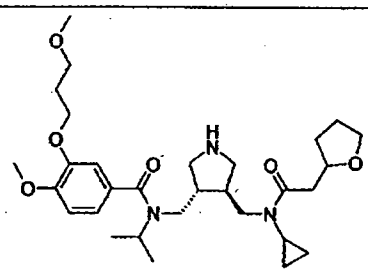
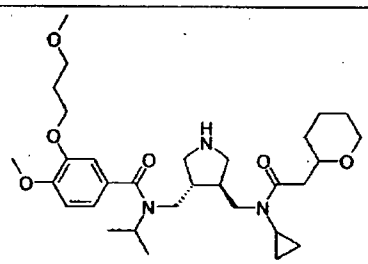
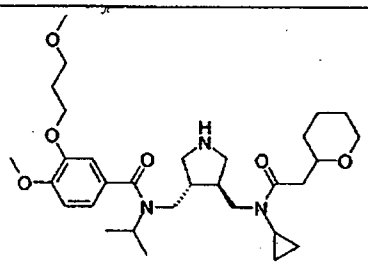
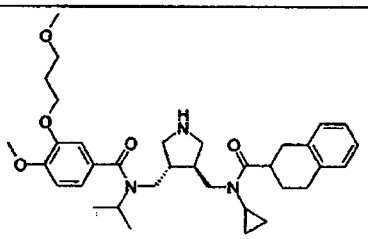
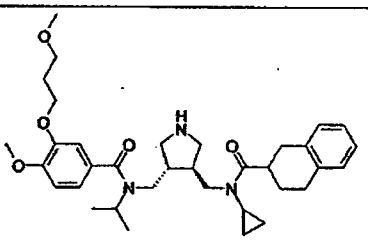
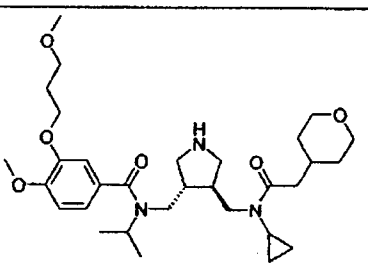
46	(3S*, 4S*)		587.3	4.79[e]
47	(3S*, 4S*)		582.3	4.58[e]
48	(3S*, 4S*)		588.2	4.36[f]
49	(3S*, 4S*)		606.2	4.99[e]
50	(3S*, 4S*)		620.2	4.67[f]
51	(3S*, 4S*)		688.2	5.58[e]

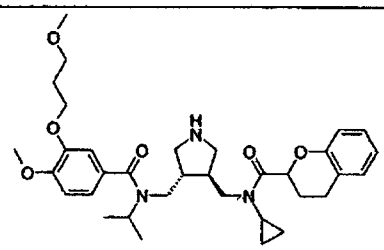
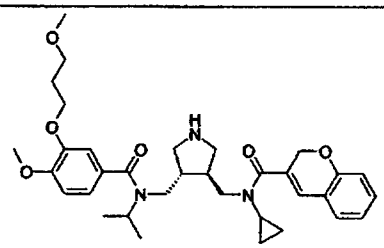
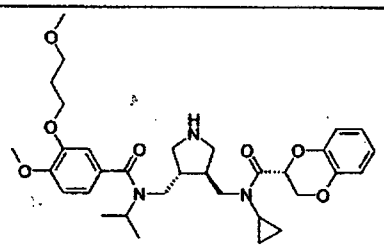
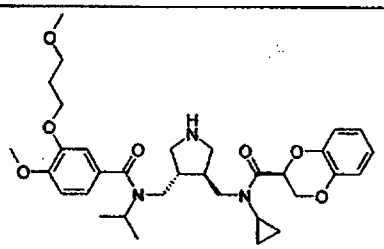
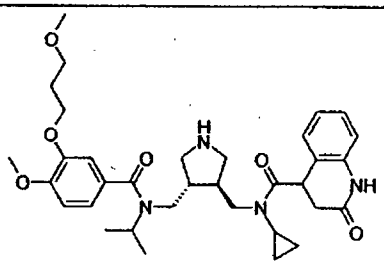
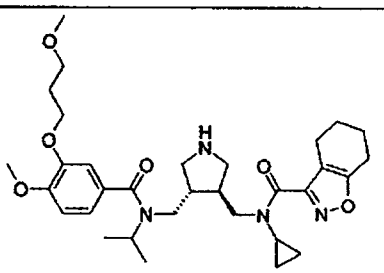
52	(3S*, 4S*)		607.4	3.96[e]
53	(3S*, 4S*)		646.4	5.18[e]
54	(3S*, 4S*)		602.2	4.30[f]
55	(3S*, 4S*)		637.3	2.93[f]
56	(3S*, 4S*)		577.3	4.91[e]
57	(3S*, 4S*)		577.3	4.54[e]

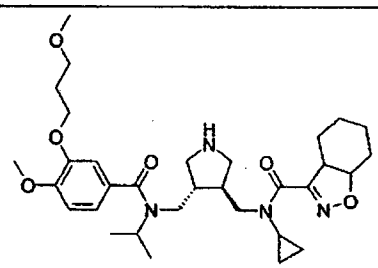
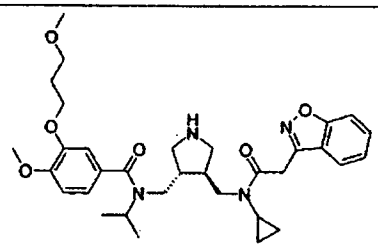
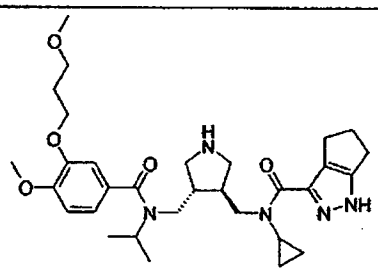
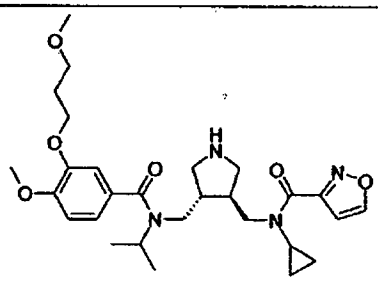
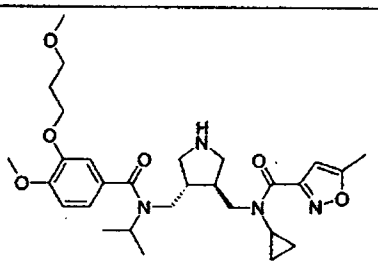
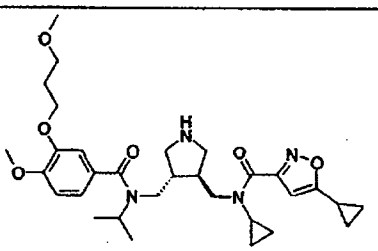
58	(3S,4S)		596.2	3.76[f]
59	(3S*, 4S*)		602.2	5.11[f]
60	(3S,4S)		568.2	4.04[f]
61	(3S*, 4S*)		566.4	4.96[e]
62	(3S*, 4S*)		566.4	4.92[e]
63	(3S,4S)		568.2	3.54[f]

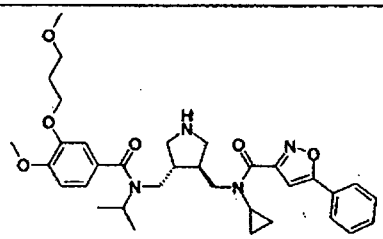
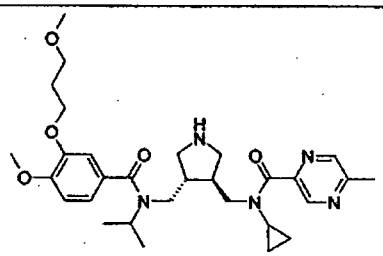
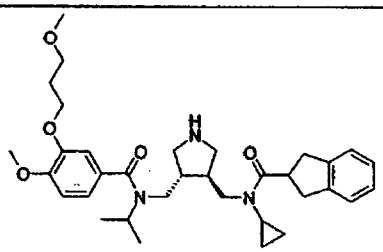
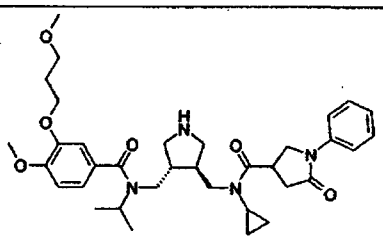
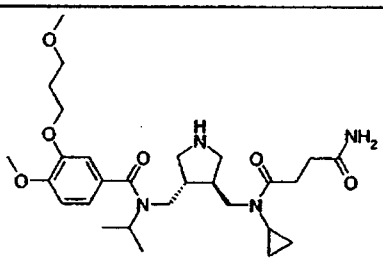
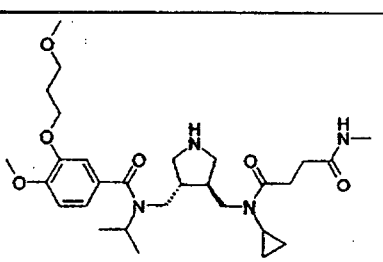
64	(3S,4S)		568.2	3.52[f]
65	(3S,4S)		582.2	3.78[f]
66	(3S,4S)		582.2	3.80[f]
67	(3S*,4S*)		532.2	3.29[f]
68	(3S*,4S*)		532.2	3.32[f]
69	(3S,4S)		546.2	3.40[f]

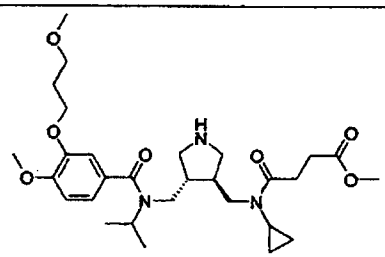
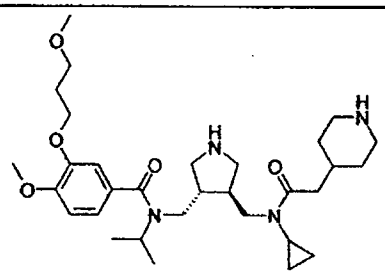
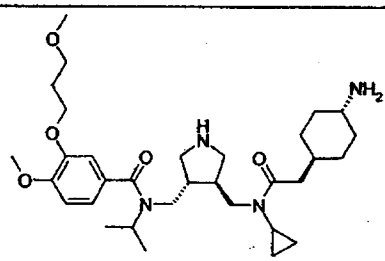
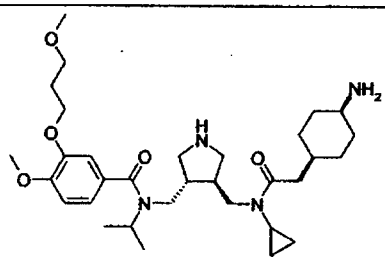
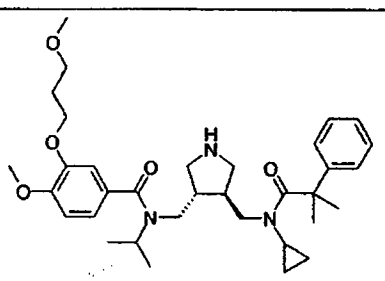
70	(3S,4S)		546.2	3.41[f]
71	(3S*, 4S*)		546.4	4.21[e]
72	(3S,4S)		560.2	3.10[f]
73	(3S,4S)		574.2	3.82[f]
74	(3S,4S)		574.2	3.60[f]
75	(3S,4S)		546.2	3.46[f]

76	(3S,4S)		546.2	3.48[f]
77	(3S,4S)		560.2	3.75[f]
78	(3S,4S)		560.2	3.72[f]
79	(3S,4S)		592.2	4.47[f]
80	(3S,4S)		592.2	4.46[f]
81	(3S*, 4S*)		560.4	4.08[e]

82	(3S,4S)		594.2	4.28[f]
83	(3S,4S)		592.2	4.20[f]
84	(3S,4S)		596.2	4.80[e]
85	(3S,4S)		596.2	4.80[e]
86	(3S,4S)		607.2	3.43[f] /3.50[f]
87	(3S,4S)		583.2	4.00[f]

88	(3S,4S)		585.3	4.73[e]
89	(3S,4S)		593.2	4.02[f]
90	(3S*, 4S*)		568.3	4.21[e]
91	(3S*, 4S*)		529.2	3.37[f]
92	(3S*, 4S*)		543.2	4.39[e]
93	(3S*, 4S*)		569.2	3.88[f]

94	(3S,4S)		605.2	4.97[e]
95	(3S*, 4S*)		554.2	4.15[e]
96	(3S,4S)		578.2	4.38[f]
97	(3S*, 4S*)		621.3	4.52[e]
98	(3S*, 4S*)		533.2	2.91[f]
99	(3S*, 4S*)		547.2	3.00[f]

100	(3S*, 4S*)		548.2	3.49[f]
101	(3S,4S)		559.4	3.75[e]
102	(3S,4S)		573.4	3.81[e]
103	(3S,4S)		573.4	3.81[e]
104	(3S,4S)		580.2	4.35[f]

[a] t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de

CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto).

[b] t_R (Columna Waters Symmetry C18, del 10 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/H_2O, 2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 0.6 mililitros/minuto).

[c] t_R (Columna Waters Symmetry C18, del 5 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/H_2O, 2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 0.6 mililitros/minuto).

[d] t_R (Columna Waters Symmetry C18, del 20 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/H_2O, 2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 0.6 mililitros/minuto).

[e] t_R (Columna Nucleosil C18HD, del 5 al 100 por ciento de CH_3CN/H_2O/6 minutos, 95 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto).

[f] t_R (HPLC, columna Nucleosil C18HD, del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto).

Los materiales de inicio se preparan como sigue:

Para los Ejemplos 73 y 74: El terbutil-éster del ácido (3R,4R)-3-{[ciclopropil-cis-(4-metoxi-ciclohexan-carbonil)-amino]-metil}-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico y el terbutil-éster del ácido (3R,4R)-3-{[ciclopropil-trans-(4-metoxi-ciclohexan-carbonil)-amino]-metil}-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico, se separan mediante HPLC quiral de la mezcla diaestereoisomérica (0.77 gramos) sobre una Chiralpak AD (20 µM; columna de 50 x 500 milímetros), utilizando n-hexano/isopropanol, 4:1, como eluyente (velocidad de flujo: 100 mililitros/minuto, UV 210 nanómetros).

Para los Ejemplos 75 y 76: El terbutil-éster del ácido (3R,4R)-3-{[ciclopropil-(2-tetrahidro-furan-2(R)-il-acetil)-amino]-metil}-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico y el terbutil-éster del ácido (3R,4R)-3-{[ciclopropil-(2-tetrahidro-furan-2(S)-il-acetil)-amino]-metil}-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico, se separan mediante HPLC quiral de la mezcla diaestereoisomérica (0.34 gramos) sobre una Chiralpak AD (20 µM; columna de 50 x 500 milímetros), utilizando n-hexano/EtOH/MeOH, 70:25:5, como eluyente (velocidad de flujo: 100 mililitros/minuto, UV 210 nanómetros).

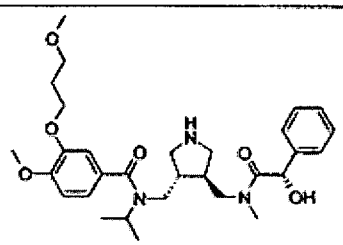
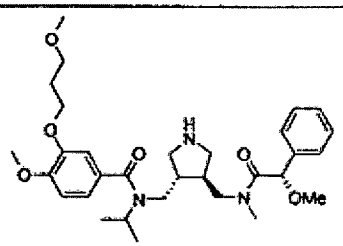
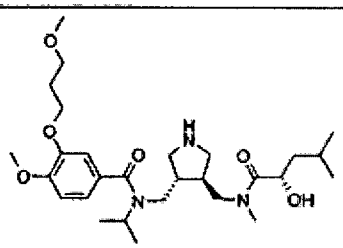
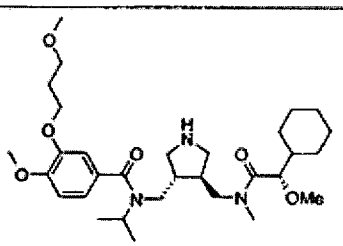
Para los Ejemplos 77 y 78: El terbutil-éster del ácido

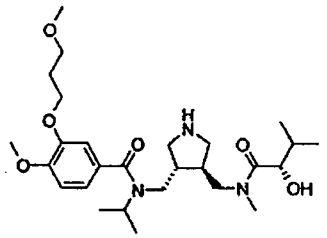
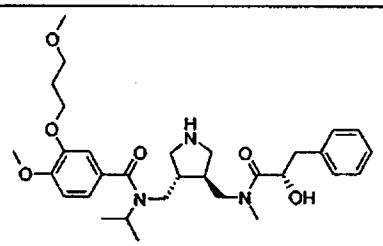
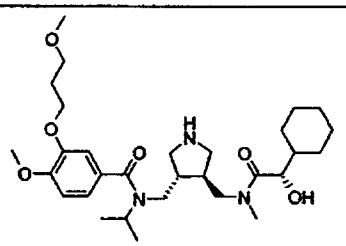
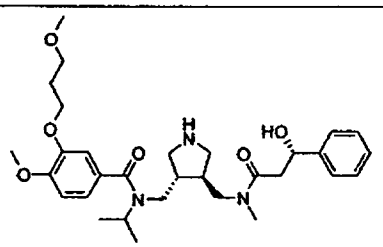
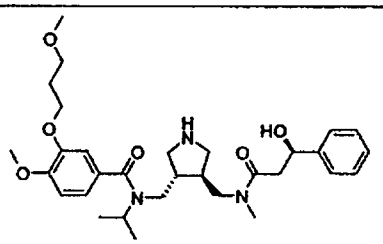
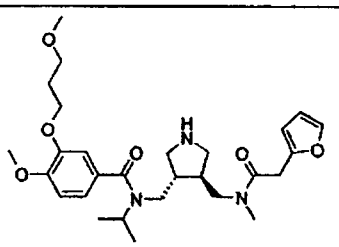
(3R,4R)-3-{[ciclopropil-(2-tetrahidro-piran-2(R)-il-acetil)-amino]-metil}-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico y el terbutil-éster del ácido (3R,4R)-3-{[ciclopropil-(2-tetrahidro-piran-2(S)-il-acetil)-amino]-metil}-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico, se separan mediante HPLC quiral de la mezcla diaestereoisomérica (0.32 gramos) sobre una Chiralpak AD (20 µM; columna de 50 por 500 milímetros), utilizando un gradiente de 90:10 a 85:15 de n-hexano/EtOH (después de 30 minutos) como eluyente (velocidad de flujo: 120 mililitros/ minuto, UV 210 nanómetros).

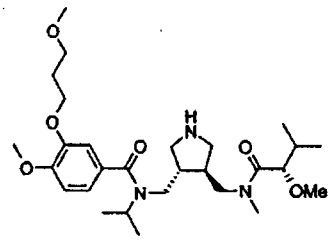
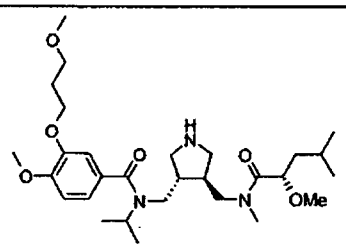
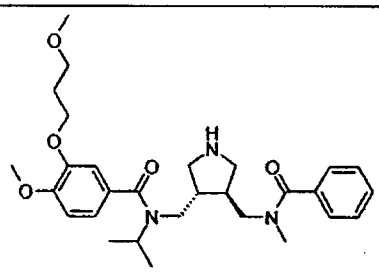
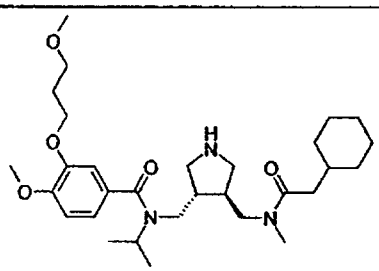
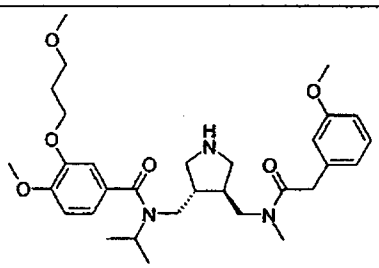
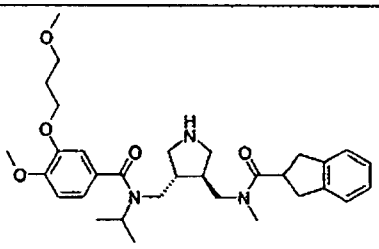
Para los Ejemplos 79 y 80: El terbutil-éster del ácido (3R,4R)-3-{[ciclopropil-(1,2,3,4-tetrahidro-naftalen-2(R)-carbonil)-amino]-metil}-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico y el terbutil-éster del ácido (3R,4R)-3-{[ciclopropil-(1,2,3,4-tetrahidro-naftalen-2(S)-carbonil)-amino]-metil}-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico, se separan mediante HPLC quiral de la mezcla diaestereoisomérica (0.42 gramos) sobre una Chiralpak AD (10 micras; columna de 50 x 500 milímetros), utilizando n-hexano/EtOH, 4:1, como eluyente (velocidad de flujo: 50 mililitros/minuto, UV 210 nanómetros).

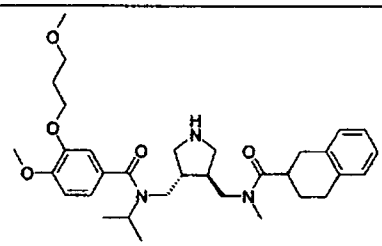
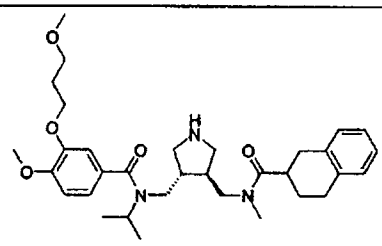
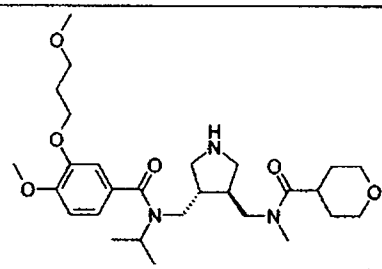
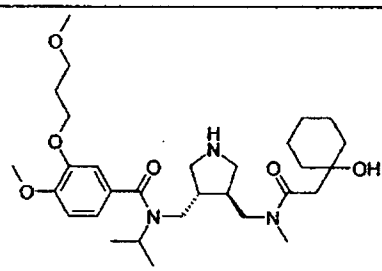
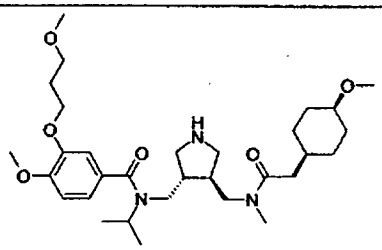
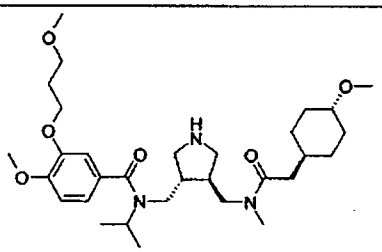
Los siguientes Ejemplos se preparan de acuerdo con los procedimientos descritos anteriormente en los Ejemplos 8, 9, 10, 11, 12, y 13:

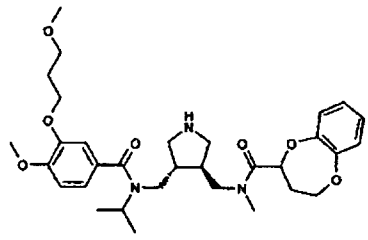
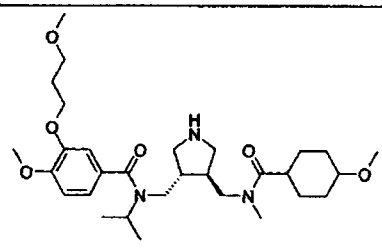
Tabla 2

Ejemplo	Configuración	Estructura	$[M+H]^+$	t_R (HPLC)
105	(3S, 4S)		542.2	4.29[a]
106	(3S, 4S)		556.3	4.43[a]
107	(3S, 4S)		522.2	3.48[d]
108	(3S, 4S)		562.3	2.83[c]

109	(3S, 4S)		508.3	2.59[c]
110	(3S, 4S)		556.3	2.17minb c
111	(3S, 4S)		548.3	2.79[c]
112	(3S, 4S)		556.3	1.98[b]
113	(3S, 4S)		556.3	1.77[b]
114	(3S, 4S)		516.3	2.60[c]

115	(3S, 4S)		522.3	1.75[b]
116	(3S, 4S)		536.3	2.39[b]
117	(3S*, 4S*)		512.2	4.09[e]
118	(3S, 4S)		532.4	4.86[e]
119	(3S*, 4S*)		556.3	4.29[e]
120	(3S,4S)		552.2	4.04[f]

121	(3S,4S)		566.2	4.16[f]
122	(3S,4S)		566.2	4.17[f]
123	(3S*, 4S*)		520.3	3.74[e]
124	(3S,4S)		548.2	3.63[f]
125	(3S,4S)		562.3	3.55[f]
126	(3S,4S)		562.2	3.47[f]

127	(3S,4S)		584.3	5.11[f]
128 129	(3S,4S)		548.2	3.25[f] 3.41[f]

[a] t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto).

[b] t_R (Columna Waters Symmetry C18, del 20 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/H_2O, 2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 0.6 mililitros/minuto).

[c] t_R (Columna Waters Symmetry C18, del 5 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/H_2O, 2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 0.6 mililitros/minuto).

[d] t_R (Columna Nucleosil C18HD, del 20 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/H_2O, 2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 0.6 mililitros/minuto).

[e] t_R (HPLC, columna Nucleosil C18HD, del 5 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto).

[f] t_R (HPLC, columna Nucleosil C18HD, del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto).

Los materiales de inicio se preparan como sigue:

Para los Ejemplos 121 y 122: El terbutil-éster del ácido (3R,4R)-3-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-4-{[metil-(1,2,3,4-tetrahidro-naftalen-2(R)-carbonil-amino]-metil}-pirrolidin-1-carboxílico y el terbutil-éster del ácido (3R,4R)-3-{[isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-4-{[metil-(1,2,3,4-tetrahidro-naftalen-2(S)-carbonil-amino]-metil}-pirrolidin-1-carboxílico, se separan mediante HPLC quiral de la mezcla diaestereoisomérica (0.32 gramos) sobre una Chiralpak AD (20 µM; columna de 50 x 500 milímetros), utilizando n-hexano/EtOH, 1:1, como eluyente (velocidad de flujo: 50 mililitros/minuto, UV 210 nanómetros).

Para los Ejemplos 128 y 129: El terbutil-éster del ácido (3R,4R)-3-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-

amino}-metil)-4-{[cis-(4-metoxi-ciclohexan-carbonil)-metil-amino]-metil}-pirrolidin-1-carboxílico y el terbutil-éster del ácido (3R,4R)-3-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-4-{[trans-(4-metoxi-ciclo-hexan-carbonil)-metil-amino]-metil}-pirrolidin-1-carboxílico, se separan mediante HPLC quiral de la mezcla diaestereoisomérica (0.32 gramos) sobre una Chiralpak AD (20 µM; columna de 50 x 500 milímetros), utilizando n-hexano/EtOH, 1:1, como eluyente (velocidad de flujo: 50 mililitros/minuto, UV 210 nanómetros).

Los siguientes intermediarios se preparan de conformidad con lo anterior:

Ácido 3-acetil-amino-3-metil-butírico

Se agregan en secuencia trietil-amina (1.8 mili-litros, 12.8 milimoles), anhídrido acético (1.2 mililitros, 12.8 milimoles), y DMAP (10 miligramos, 0.09 milimoles), a una suspensión de ácido 3-amino-3-metil-butírico (1.00 gramos, 8.5 milimoles) en tetrahidrofurano (100 mililitros). Después de calentar a 60°C durante 3 horas, se agrega AcOEt, y la fase orgánica se lava con HCl 1N. El secado (Na_2SO_4), la filtración, y la evaporación del solvente, producen el producto deseado. MS (LC-MS) $[M+H]^+$ = 160.1. t_R (HPLC, columna Waters Symmetry C18, del 20 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/H_2O, 2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 0.6 mililitros/minuto): 0.40 minutos.

Ácido (1-acetil-amino-ciclopentil)-acético

Se agregan en secuencia trietil-amina (1.2 mili-litros, 8.4 milimoles), anhídrido acético (0.8 mililitros, 8.4 milimoles), y DMAP (10 miligramos, 0.09 milimoles), a una suspensión de ácido (1-amino-ciclopentil)-acético (1.00 gramos, 5.6 milimoles) en tetrahidrofurano (30 mililitros). Después de calentar a 60°C durante 2 horas, se agrega AcOEt, y la fase orgánica se lava con HCl 1N. El secado (Na_2SO_4), la filtración, y la evaporación del solvente, producen el producto deseado. MS (LC-MS) $[M+H]^+$ = 186.1. t_R (HPLC, columna Waters Symmetry C18, del 80 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/H_2O, 2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 0.6 mililitros/minuto): 0.53 minutos.

Ácido (1-acetil-amino-ciclohexil)-acético

El compuesto del título se prepara de una manera análoga a la descrita para el ácido (1-acetil-amino-ciclopentil)-acético, a partir del ácido (1-amino-ciclohexil)-acético. MS (LC-MS): $[M+H]^+$ = 200.1. (HPLC, columna Waters Symmetry C18, del 20 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/H_2O, 2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 0.6 mililitros/minuto): 0.81 minutos.

Ácido (1-isobutiril-amino-ciclopentil)-acético

El compuesto del título se prepara de una manera análoga a

la descrita para el ácido (1-acetil-amino-ciclopentil)-acético, a partir del ácido (1-amino-ciclopentil)-acético. MS (LC-MS): $[M+H]^+$ = 214.2. t_R (HPLC, columna Waters Symmetry C18, del 20 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/H_2O, 2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 0.6 mililitros/minuto): 3.08 minutos.

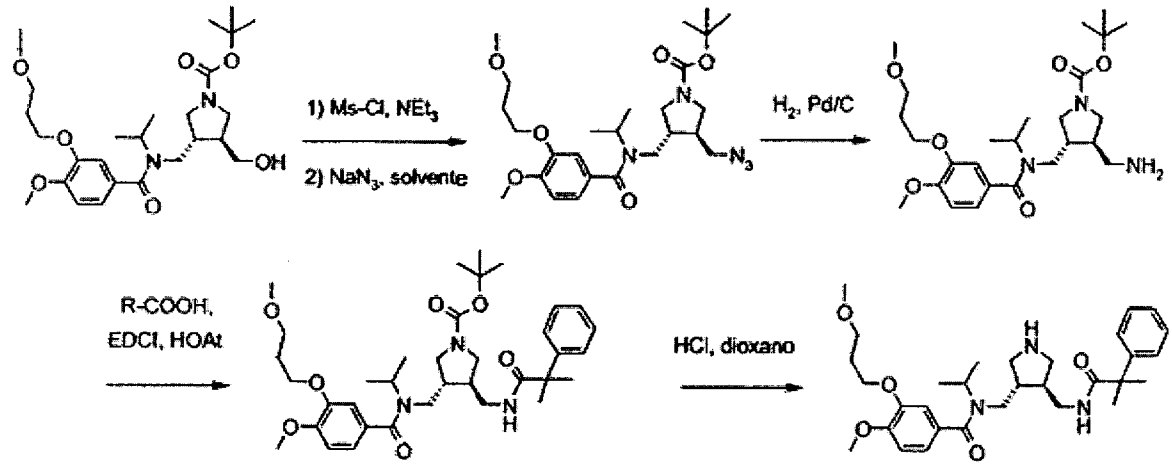
Ácido (S)-3-acetil-amino-3-fenil-propiónico

El compuesto del título se prepara de una manera análoga a la descrita para el ácido (1-acetil-amino-ciclopentil)-acético, a partir del ácido (S)-3-amino-3-fenil-propiónico. MS (LC-MS): $[M+H]^+$ = 208.2. t_R (HPLC, columna Waters Symmetry C18, del 10 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/H_2O, 2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 0.6 mililitros/minuto): 0.79 minutos.

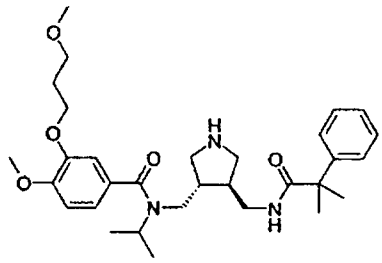
Ácido (R)-3-acetil-amino-3-fenil-propiónico

El compuesto del título se prepara de una manera análoga a la descrita para el ácido (1-acetil-amino-ciclopentil)-acético, a partir del ácido (R)-3-amino-3-fenil-propiónico. MS (LC-MS): $[M+H]^+$ = 208.2. t_R (HPLC, columna Waters Symmetry C18, del 10 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/H_2O, 2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 0.6 mililitros/minuto): 1.16 minutos.

Esquema de reacción 6



Ejemplo 130: N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-N-{(3S,4S)-4-[(2-metil-2-fenil-propionil-amino)-metil]-pirrolidin-3-ilmetil}-benzamida



El compuesto del título se prepara de acuerdo con el Esquema de reacción 6 como sigue: La solución del terbutil-éster del ácido (3R,4R)-3-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-4-[(2-metil-2-fenil-propionil-amino)-metil]-pirrolidin-1-carboxílico (227 miligramos, 0.319 mili-moles) en HCl 4N en dioxano (2 mililitros), se agita durante 6 horas a temperatura ambiente. Los volátiles se retiran mediante secado por congelación para dar el compuesto del título como un sólido blanco. MS $[M+H]^+$ = 540.2. t_R (HPLC, columna Nucleosil C18HD,

del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto): 3.91 minutos.

El material de inicio se prepara como sigue:

A. Terbutil-éster del ácido (3R,4S)-3-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-4-metan-sulfoniloxi-metil-pirrolidin-1-carboxílico.

A una solución del terbutil-éster del ácido (3S,4R)-3-hidroxi-metil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (2.32 gramos, 4.69 milimoles; Ejemplo 10, paso de reacción H), se le agrega subsecuentemente, a -20°C con agitación, NEt_3 (1.95 mililitros, 14.1 milimoles), y en una forma por goteo, cloruro de metansulfonilo (0.423 mililitros, 5.39 milimoles). La agitación se continúa durante 20 minutos a -20°C, la mezcla se diluye entonces con CH_2Cl_2, y la capa orgánica se lava con HCl 2N, se seca (Na_2SO_4), y se evapora a sequedad, para dar el compuesto del título crudo como un aceite amarillento. TLC, R_f (hexano/AcOEt, 1:3) = 0.13.

B. Terbutil-éster del ácido (3S,4R)-3-azido-metil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico.

A una solución del terbutil-éster del ácido (3R,4S)-3-

({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-4-metan-sulfoniloxi-metil-pirrolidin-1-carboxílico (2.7 gramos, 4.71 milimoles) en dimetil-formamida (20 mililitros), se le agrega, en una porción, NaN_3 (774 miligramos, 11.8 milimoles), y la mezcla se agita a 70°C durante la noche. Después de enfriarse a temperatura ambiente, se agrega una solución acuosa saturada de $NaHCO_3$, seguido por extracción con dietil-éter. Los orgánicos combinados se lavan con salmuera, se secan sobre Na_2SO_4, y se concentran. El producto crudo se purifica mediante RP-HPLC sobre una columna PrepC_{18} OBD (dimensiones: 30 x 100 milímetros; tamaño de partículas de 5 micras, SunFire Ltd.), y utilizando un gradiente del 95 al 5 por ciento de MeCN/H_2O, 5:95 (conteniendo ácido trifluoroacético al 0.1 por ciento) hasta MeCN/H_2O, 95:5 (conteniendo ácido trifluoroacético al 0.1 por ciento) durante 20 minutos, para dar el compuesto del título como un aceite incoloro. TLC, R_f (hexano/AcOEt, 1:3) = 0.31. MS: 520.2 $[M+H]^+$. t_R (HPLC, columna Nucleosil C18HD, del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto): 5.04 minutos.

C. Terbutil-éster del ácido (3R,4R)-3-amino-metil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico.

Una solución del terbutil-éster del ácido (3S,4R)-3-azido-

metil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (1.86 gramos, 3.58 milimoles) en MeOH (40 mililitros), se hidrogena durante la noche en la presencia de Pd/C al 10 por ciento (0.6 gramos; Engelhard 4505) a temperatura ambiente bajo presión atmosférica, para dar, después de la filtración y el secado al vacío, el compuesto del título como un aceite incoloro. MS 494.2 $[M+H]^+$. t_R (HPLC, columna Nucleosil C18HD, del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto): 3.73 minutos.

D. Terbutil-éster del ácido (3R,4R)-3-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-4-[(2-metil-2-fenil-propionil-amino)-metil]-pirrolidin-1-carboxílico.

A una solución del terbutil-éster del ácido (3R,4R)-3-amino-metil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (200 mili-gramos, 0.405 milimoles) y ácido α,α-dimetil-fenil-acético (101 miligramos, 0.608 milimoles) en CH_2Cl_2(3 mililitros), se le agregan subsecuentemente Et_3N (0.085 mililitros, 0.608 milimoles), 1-hidroxi-7-aza-benzotriazol (84 miligramos, 0.608 milimoles; comercialmente disponible en ABCR, AV24631), y N-(3-dimetil-amino-propil)-N'-etil-carbodi-imida HCl (118 miligramos, 0.608 milimoles). La agitación se continúa durante la noche a temperatura ambiente, luego la mezcla se

diluye con CH_2Cl_2, y la capa orgánica se lava subsecuentemente con HCl 2N, $NaHCO_3$ acuoso saturado, y salmuera, se seca ($MgSO_4$), y se concentra. La purificación mediante RP-HPLC sobre una columna PrepC_{18} OBD (dimensiones: 30 x 100 milímetros; tamaño de partículas de 5 micras, SunFire Ltd.), y utilizando un gradiente del 95 al 5 por ciento de MeCN/H_2O, 5:95 (conteniendo ácido trifluoro-acético al 0.1 por ciento) hasta MeCN/H_2O, 95:5 (conteniendo ácido trifluoroacético al 0.1 por ciento) durante 20 minutos, da el compuesto del título como un aceite incoloro. MS $[M]^+$ = 640.2. t_R (HPLC, columna Nucleosil C18HD, del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto): 5.2 minutos.

De una manera similar a la descrita en el Ejemplo 9 para el paso de reacción J, se preparan los siguientes materiales de inicio, los cuales se utilizan para la preparación de los Ejemplos 137-148 enlistados en la Tabla 3:

N-((3S*,4R*)-4-etil-amino-metil-pirrolidin-3-ilmetil)-N-iso-propil-4-metoxi-3-(3-metoxi-propoxi)-benzamida: El compuesto del título se prepara a partir del terbutil-éster del ácido (3S*,4R*)-3-formil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (0.75 gramos, 1.52 milimoles), solución 2N de etil-amina en MeOH (3.805 mililitros, 7.61

milimoles), y $NaBH_4$ (0.115 gramos, 3.04 milimoles), y purificación mediante cromatografía por evaporación instantánea sobre gel de sílice (CH_2Cl_2/MeOH, 96:4, luego CH_2Cl_2/MeOH (NH_3 concentrado al 10 por ciento), gradiente de 9:1 a 8:2), para dar un aceite incoloro. MS: 522.4 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18HD, del 5 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto): 4.47 minutos.

El enantiómero correspondiente de **N-((3S,4R)-4-etil-amino-metil-pirrolidin-3-ilmetil)-N-iso-propil-4-metoxi-3-(3-metoxi-propoxi)-benzamida**, se obtiene como sigue: Una solución del terbutil-éster del ácido (3S,4R)-3-formil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (1.27 gramos, 2.58 milimoles) y etil-amina gaseosa (0.704 gramos, 15.5 milimoles; Fluka 02940) en 1,2-dicloro-etano (10 mililitros), se agita a temperatura ambiente durante 30 minutos, luego se agrega triacetoxi-borohidruro de sodio (1.37 gramos, 6.45 milimoles) en una porción, y la mezcla se agita durante la noche. La fase orgánica se lava con una solución acuosa saturada de $NaHCO_3$, las capas de agua se vuelven a extraer con CH_2Cl_2, y los orgánicos combinados se secan (Na_2SO_4) y se evaporan a sequedad, para dar el compuesto del título. MS: 522.2 $[M+H]^+$.

N-((3S*,4S*)-4-ciclobutil-amino-metil-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida: a partir del

terbutil-éster del ácido (3S*,4R*)-3-formil-4-({iso-propil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (1.00 gramos, 2.03 milimoles), ciclobutil-amina (0.74 gramos, 10.2 milimoles), y $NaBH_4$ (0.154 gramos, 4.06 milimoles), para dar el compuesto del título como un aceite. TLC, R_f (hexano/AcOEt) = 0.31. MS: 548.3 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18HD, del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto): 4.28 minutos.

N-isopropil-N-[(3S*,4S*)-4-(isopropil-amino-metil)-pirrolidin-3-ilmetil]-4-metoxi-3-(3-metoxi-propoxi)-benzamida: a partir del terbutil-éster del ácido (3S*,4R*)-3-formil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (0.75 gramos, 1.52 mili-moles), isopropil-amina (0.654 mililitros, 7.61 milimoles), y $NaBH_4$ (0.115 gramos, 3.04 milimoles), y purificación mediante cromatografía por evaporación instantánea sobre gel de sílice (CH_2Cl_2/MeOH, 96:4, luego CH_2Cl_2/MeOH (NH_3 concentrado al 10 por ciento), gradiente de 9:1 a 8:2), para dar el compuesto del título como un aceite incoloro. MS: 536.4 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18HD, del 5 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto): 4.58 minutos.

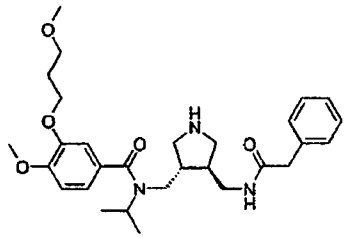
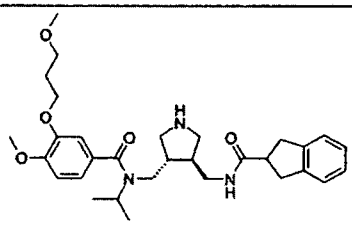
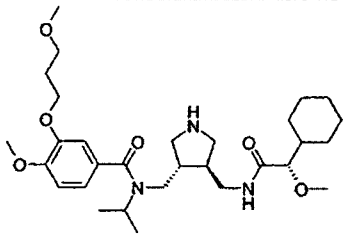
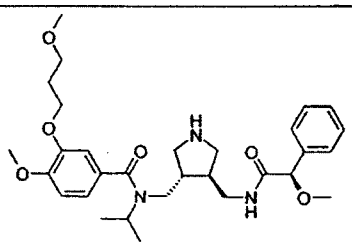
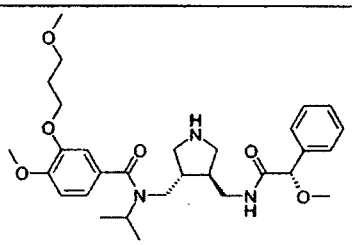
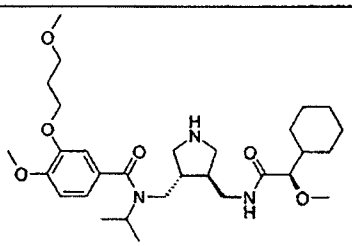
N-[(3S*,4R*)-4-(isobutil-amino-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida: a partir del terbutil-éster del ácido (3S*,4R*)-3-formil-4-({iso-propil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (0.75 gramos, 1.52 milimoles), iso-butil-amina (0.756 mililitros, 7.61 milimoles), y $NaBH_4$ (0.115 gramos, 3.04 milimoles), y purificación mediante cromatografía por evaporación instantánea sobre gel de sílice (CH_2Cl_2/MeOH, 96:4, luego CH_2Cl_2/MeOH (NH_3 concentrado al 10 por ciento), gradiente de 9:1 a 8:2), para dar el compuesto del título como un aceite incoloro. MS: 550.4 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18HD, del 5 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto): 4.74 minutos.

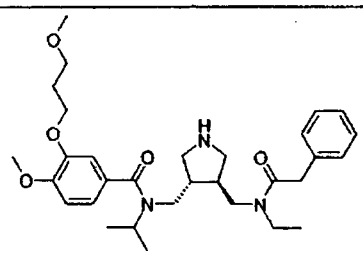
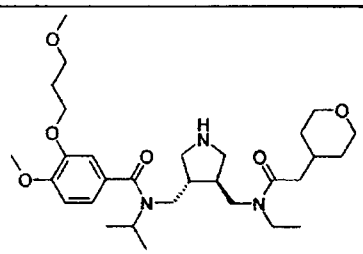
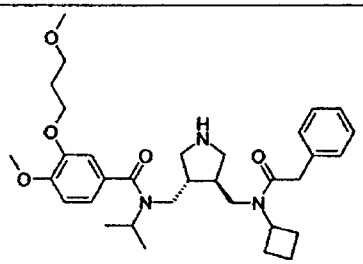
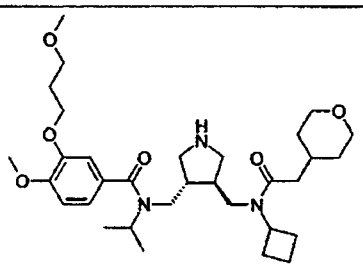
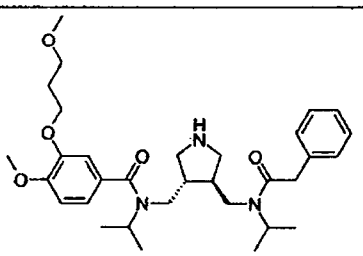
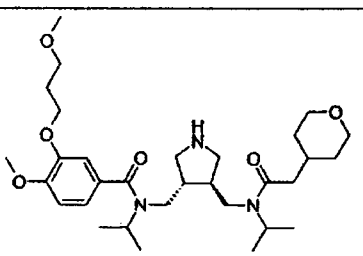
N-{(3S*,4R*)-4-[(ciclopropil-metil-amino)-metil]-pirrolidin-3-ilmetil}-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida: a partir del terbutil-éster del ácido (3S*,4R*)-3-formil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (0.75 gramos, 1.52 mili-moles), ciclopropan-metil-amina (0.652 mililitros, 7.61 mili-moles), y $NaBH_4$ (0.115 gramos, 3.04 milimoles), y purificación mediante cromatografía por evaporación instantánea sobre gel de sílice (CH_2Cl_2/MeOH, 96:4, luego CH_2Cl_2/MeOH (NH_3 concentrado al 10 por ciento), gradiente de 9:1 a 8:2), para dar el compuesto del título como un aceite incoloro.

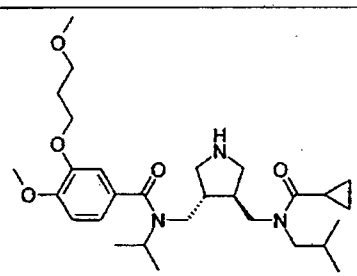
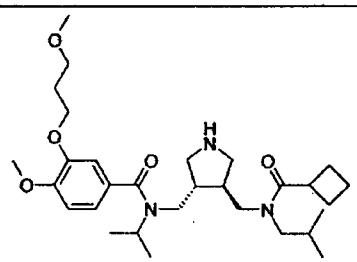
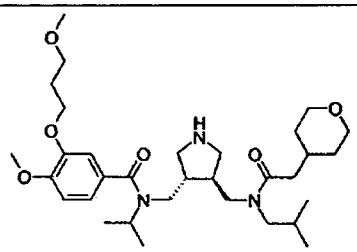
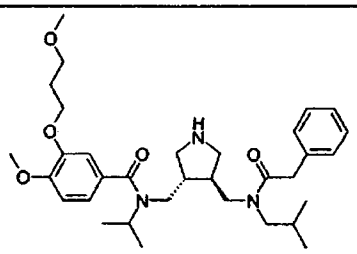
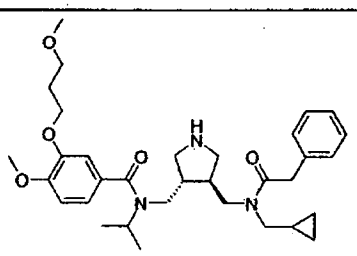
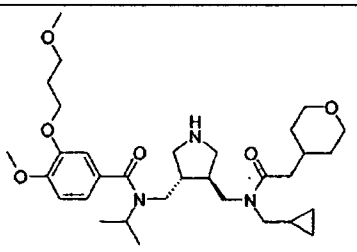
MS: 548.4 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18HD, del 5 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto): 4.66 minutos.

Los compuestos de título de la Tabla 3 se preparan de conformidad con lo anterior, a partir de los materiales de inicio descritos anteriormente:

Tabla 3

Ejemplo	Configuración	Estructura	$[M+H]^+$	t_R (HPLC)
131	(3S,4S)		512.2	3.47[b]
132	(3S,4S)		538.2	3.83[b]
133	(3S,4S)		548.2	4.00[b]
134	(3S,4S)		542.2	3.59[b]
135	(3S,4S)		542.2	3.57[b]
136	(3S,4S)		548.2	3.98[b]

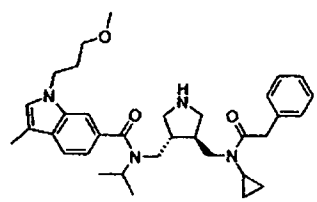
137	(3S,4S)		540.2	3.86[b]
138	(3S,4S)		548.3	4.11[a]
139	(3S*, 4S*)		566.2	4.32[b]
140	(3S*, 4S*)		574.2	3.74[b]
141	(3S*, 4S*)		554.4	4.58[a]
142	(3S*, 4S*)		562.4	4.14[a]

143	(3S*, 4S*)		532.4	4.88[a]
144	(3S*, 4S*)		518.4	4.64[a]
145	(3S*, 4S*)		576.4	4.33[a]
146	(3S*, 4S*)		568.4	4.76[a]
147	(3S*, 4S*)		566.4	4.66[a]
148	(3S*, 4S*)		574.4	4.23[a]

[a] t_R (HPLC, columna Nucleosil C18HD, del 5 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto).

[b] t_R (HPLC, columna Nucleosil C18HD, del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto).

Ejemplo 149: {(3S,4S)-4-[(ciclopropil-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-isopropil-amida del ácido 1-(3-metoxi-propil)-3-metil-1H-indol-6-carboxílico



A una solución del terbutil-éster del ácido (3R,4R)-3-[(ciclopropil-fenil-acetil-amino)-metil]-4-({isopropil-[1-(3-metoxi-propil)-3-metil-1H-indol-6-carbonil]-amino}-metil)-pirrolidin-1-carboxílico (0.26 gramos, 0.395 milimoles) en dioxano (1 mililitro), se le agrega HCl 4N en dioxano (1 mili-litro), y la solución resultante se liofiliza para proporcionar la sal de clorhidrato correspondiente. MS (LC-MS): 559 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN

y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.35 minutos.

El material de inicio se prepara como sigue:

A. Terbutil-éster del pacido (3S,4R)-3-(terbutil-di-metil-silaniloxi-metil)-4-({isopropil-[1-(3-metoxi-propil)-3-metil-1H-indol-6-carbonil]-amino}-metil)-pirrolidin-1-carboxílico.

Una mezcla del terbutil-éster del ácido (3S,4R)-3-(terbutil-dimetil-silaniloxi-metil)-4-(isopropil-amino-metil)-pirrolidin-1-carboxílico (8.5 gramos, 22 milimoles), ácido 1-(3-metoxi-propil)-3-metil-1H-indol-6-carboxílico (7.6 gramos, 30.8 milimoles), cloruro bis-(2-oxo-3-oxazolidinil)-fosfínico (7.84 gramos, 30.8 milimoles), y trietil-amina (12.3 mililitros, 88 milimoles) en CH_2Cl_2 (425 mililitros), se pone a reflujo durante la noche bajo una atmósfera de nitrógeno, y luego se apaga mediante la adición de una solución acuosa saturada de $NaHCO_3$. La capa orgánica se separa, y la fase acuosa se extrae 3 veces con AcOEt. Los extractos orgánicos combinados se concentran al vacío. El aceite residual se recupera en una mezcla de tetrahidrofurano y MeOH, se agrega NaOH 1N para disociar el producto secundario de anhídrido, y la mezcla se agita durante 3 horas. Los solventes se concentran, se agrega CH_2Cl_2, y las capas se separan. Entonces la acuosa se retro-extrae dos veces con CH_2Cl_2, y los extractos orgánicos combinados se lavan con salmuera, se secan sobre Na_2SO_4, se filtran, y se concentran. El producto crudo se utiliza en el

siguiente paso sin mayor purificación. TLC, R_f (AcOEt) = 0.6. MS (LC-MS): 516.3 $[M-Boc+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 8.60 minutos.

B. Terbutil-éster del ácido (3S,4R)-3-hidroxi-metil-4-({isopropil-[1-(3-metoxi-propil)-3-metil-1H-indol-6-carbonil]-amino}-metil)-pirrolidin-1-carboxílico.

A una solución del terbutil-éster del ácido (3S,4R)-3-(terbutil-dimetil-silaniloxi-metil)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (13.8 gramos, 33 milimoles) en MeCN (350 mili-litros), se le agrega hidrato de fluoruro de tetraetil-amonio (6.6 gramos, 44 milimoles) bajo una atmósfera de nitrógeno. La mezcla de reacción se pone a reflujo durante 3 horas. Se agregan agua y AcOEt, las capas se separan, y la acuosa se extrae dos veces con AcOEt. Los extractos orgánicos combinados se secan (Na_2SO_4), se filtran, y el solvente se retira al vacío. El producto crudo se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente: CH_2Cl_2/MeOH, de 100:0 a 90:10), para dar el producto del título. TLC, R_f (CH_2Cl_2/MeOH, 95:5) = 0.2. MS (LC-MS): 402.2 $[M+H-Boc]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido

trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 6.85 minutos.

C. Terbutil-éster del ácido (3S,4R)-3-formil-4-({iso-propil-[1-(3-metoxi-propil)-3-metil-1H-indol-6-carbonil]-amino}-metil)-pirrolidin-1-carboxílico.

El compuesto del título se prepara de una manera análoga a la descrita para el compuesto del título según I en el Esquema de reacción 5, a partir del terbutil-éster del ácido (3S,4R)-3-hidroxi-metil-4-({isopropil-[1-(3-metoxi-propil)-3-metil-1H-indol-6-carbonil]-amino}-metil)-pirrolidin-1-carboxílico. TLC, R_f (CH_2Cl_2/MeOH, 95:5) = 0.6. t_R (HPLC, columna C18, del 5 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto): 5.11 minutos.

D. Terbutil-éster del ácido (3R,4R)-3-ciclopropil-amino-metil-4-({isopropil-[1-(3-metoxi-propil)-3-metil-1H-indol-6-carbonil]-amino}-metil)-pirrolidin-1-carboxílico.

A una solución del terbutil-éster del ácido (3S,4R)-3-formil-4-({isopropil-[1-(3-metoxi-propil)-3-metil-1H-indol-6-carbonil]-amino}-metil)-pirrolidin-1-carboxílico (6 gramos, 10.9 milimoles) en dicloro-etano (100 mililitros), se le agregan ciclopropil-amina (0.85 mililitros, 12 milimoles) y $NaBH(OAc)_3$ (4.32 gramos, 15.3 milimoles). La solución se agita a temperatura ambiente durante la noche, y luego se diluye con CH_2Cl_2. Se agrega una solución saturada de $NaHCO_3$, las capas se separan, y la acuosa se extrae

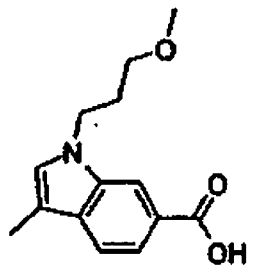
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dos veces con CH_2Cl_2. Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran, y se concentran al vacío. El material crudo se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente: AcOEt/ MeOH, de 100:0 a 85:15), para dar el compuesto del título. TLC, R_f (AcOEt) = 0.1. MS (LC-MS): 541.3 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.52 minutos.

E. Terbutil-éster del ácido (3R,4R)-3-[(ciclopropil-fenil-acetil-amino)-metil]-4-({isopropil-[1-(3-metoxi-propil)-3-metil-1H-indol-6-carbonil]-amino}-metil)-pirrolidin-1-carboxílico.

El compuesto del título se prepara de una manera análoga a la descrita para el compuesto del título según K en el Ejemplo 9 (Esquema de reacción 5), a partir del terbutil-éster del ácido (3R,4R)-3-ciclopropil-amino-metil-4-({isopropil-[1-(3-metoxi-propil)-3-metil-1H-indol-6-carbonil]-amino}-metil)-pirrolidin-1-carboxílico. MS (LC-MS): 658.9 $[M-Boc+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 6.69 minutos.

Ácido 1-(3-metoxi-propil)-3-metil-1H-indol-6-carboxílico.



Metil-éster del ácido 3-metil-1H-indol-6-carboxílico.

Una mezcla del metil-éster del ácido 3-formil-1H-indol-6-carboxílico (5 gramos, 24.6 milimoles), ácido p-toluen-sulfónico (704 miligramos, 3.7 milimoles), y p-toluen-sulfonil-hidrazida (5.49 gramos, 29.5 milimoles) en una mezcla de dimetil-formamida (50 mililitros) y sulfolano (25 mililitros), se calienta a 100°C durante 15 minutos. Entonces se enfría a temperatura ambiente, antes de la adición de ciano-borohidruro de sodio (6.2 gramos, 98.4 milimoles, porciones de 2 gramos después de intervalos de 10 minutos). La mezcla resultante se calienta a 100°C durante 2 horas, se enfría a temperatura ambiente, y se vierte en una mezcla de hielo y agua (250 mililitros), conduciendo a un precipitado blanco. Se agrega agua (500 mililitros), y la mezcla se agita durante 30 minutos antes de la filtración. El sólido grisáceo se lava con agua tibia. Se agrega tolueno, y se retira mediante evaporación giratoria, para proporcionar el compuesto del título como un sólido amarillo. TLC, R_f (hexano/AcOEt, 4:1) = 0.3. MS (LC-MS): $[M+H]^+$ = 188.1. t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O

conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.13 minutos.

Metil-éster del ácido 1-(3-metoxi-propil)-3-metil-1H-indol-6-carboxílico.

A una solución del metil-éster del ácido 3-metil-1H-indol-6-carboxílico (2.5 gramos, 13.2 milimoles) en dimetil-formamida (25 mililitros), se le agrega lentamente una solución de NaH (580 miligramos, 14.5 milimoles, dosificación al 60 por ciento en grasa) en dimetil-formamida (25 mililitros) bajo una atmósfera de N_2. La mezcla se agita a 80°C durante 20 minutos, y se enfría a temperatura ambiente antes de la adición de 1-bromo-3-metoxi-propano (4.04 gramos, 26.4 milimoles). La mezcla resultante se agita durante 24 horas. Se agregan 1-bromo-3-metoxi-propano (2.02 gramos, 13.2 milimoles) y NaH (580 miligramos, 14.5 milimoles), y la mezcla se agita adicionalmente durante 24 horas para terminar la reacción. El solvente se concentra bajo presión reducida, y la mezcla se diluye con AcOEt. Se agrega una solución acuosa saturada de $NaHCO_3$, las capas se separan, y la acuosa se retro-extrae con AcOEt. Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran, y se concentran. El residuo crudo se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente: ciclo-hexano/AcOEt, 80:20), para dar el compuesto del título. MS (LC-MS): 262.0 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3

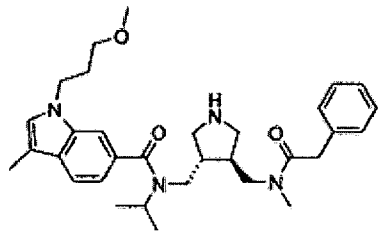
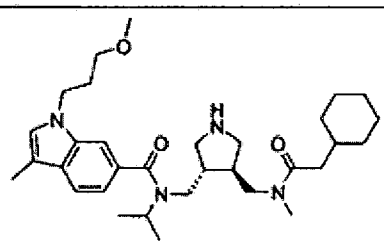
minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.80 minutos.

Ácido 1-(3-metoxi-propil)-3-metil-1H-indol-6-carboxílico.

A una solución de metil-éster del ácido 1-(3-metoxi-propil)-3-metil-1H-indol-6-carboxílico (1.56 gramos, 6.3 mili-moles) en MeOH (20 mililitros) y H_2O (1 mililitro), se le agrega NaOH (756 miligramos, 18.9 milimoles), y la mezcla se agita a 50°C durante la noche. Luego se neutraliza mediante la adición de agua y HCl 1.0 M (3 equivalentes, 18.9 milimoles). Se agrega CH_2Cl_2, las capas se separan, y la acuosa se extrae dos veces con CH_2Cl_2. Las capas orgánicas combinadas se secan sobre Na_2SO_4, se filtran, y se concentran bajo presión reducida. El material crudo se obtiene en una forma pura, y se utiliza en el siguiente paso sin purificación. MS (LC-MS): 248.0 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 4.93 minutos.

Los siguientes Ejemplos se preparan de acuerdo con los procedimientos descritos anteriormente para el Ejemplo 149:

Tabla 4

Ejemplo	Configuración	Estructura	$[M+H]^+$	t_R (HPLC)
150	(3S, 4S)		533	5.20[a]
151	(3S, 4S)		539	5.64[a]

[a] t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto).

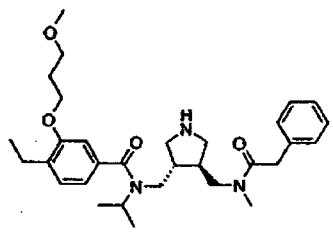
Los materiales de inicio de los compuestos del título en la Tabla 4, se preparan como sigue:

{(3S,4S)-4-[(metil-fenil-acetil-amino)-metil]-pirrolidin-3-il-metil}-isopropil-amida del ácido 1-(3-metoxi-propil)-3-metil-1H-indol-6-carboxílico.

De una manera similar a la descrita en el Ejemplo 9 para el paso de reacción J, se prepara el siguiente material de inicio a partir del terbutil-éster del ácido (3S,4R)-3-formil-4-({isopropil-[1-(3-metoxi-propil)-3-metil-1H-indol-6-carbonil]-amino}-metil)-

pirrolidin-1-carboxílico (preparado según C en el Ejemplo 151) (3 gramos, 5.4 milimoles), una solución 2N de metil-amina en MeOH (13.5 mililitros, 27 mili-moles), y $NaBH_4$ (0.408 gramos, 10.8 milimoles), y purificación mediante cromatografía por evaporación instantánea sobre gel de sílice (CH_2Cl_2/MeOH, 90:10, luego AcOEt/MeOH/NH_4OH, 89:10:1), para dar un aceite incoloro. MS: 515.0 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.41 minutos.

Ejemplo 152: 4-etil-N-isopropil-3-(3-metoxi-propoxi)-N-{(3S,4S)-4-[(metil-fenil-acetil-amino)-metil]-pirrolidin-3-il-metil}-benzamida



A una solución del terbutil-éster del ácido (3R,4R)-3-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-4-[(metil-fenil-acetil-amino)-metil]-pirrolidin-1-carboxílico (0.330 gramos, 0.529 milimoles) en dioxano (2 mililitros), se le agrega HCl 4N en dioxano (2 mililitros), y la solución resultante se liofiliza para proporcionar la sal de clorhidrato correspondiente. MS (LC-MS):

524.3 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.94 minutos.

El material de inicio se prepara de una manera similar a la descrita en el Ejemplo 149, pasos de reacción A a E, como sigue:

A. Terbutil-éster del ácido (3S,4R)-3-(terbutil-dimetil-silaniloxi-metil)-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-1-carboxílico.

A partir del terbutil-éster del ácido (3S,4R)-3-(terbutil-dimetil-silaniloxi-metil)-4-(isopropil-amino-metil)-pirrolidin-1-carboxílico (8.5 gramos, 22 milimoles), ácido 4-etil-3-(3-metoxi-propoxi)-benzoico (5.76 gramos, 24.2 mili-moles), BOPCl (6.16 gramos, 24.2 milimoles), y trietil-amina (12.3 gramos, 88 milimoles). TLC, R_f (CH_2Cl_2/MeOH, 95:5) = 0.32. t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 8.81 minutos. MS (LC-MS): $[M-H\text{-}BOC]^+$ 507.3.

B. Terbutil-éster del ácido (3R,4S)-3-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-4-hidroxi-metil-pirrolidin-1-carboxílico.

A partir del terbutil-éster del ácido (3S,4R)-3-(ter-butil-dimetil-silaniloxi-metil)-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-1-carboxílico (13.1 gramos, 21.6 milimoles) y TBAF (17 gramos, 54 milimoles), y purificación mediante cromatografía por evaporación instantánea sobre gel de sílice (CH_2Cl_2/MeOH, 95:5), para dar el compuesto del título como un aceite amarillo. TLC, R_f (AcOEt) = 0.4. MS (LC-MS): 437.3 $[M+H-tBu]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 6.74 minutos.

C. Terbutil-éster del ácido (3R,4S)-3-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-4-formil-pirrolidin-1-carboxílico.

A partir del terbutil-éster del ácido (3R,4S)-3-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-4-hidroxi-metil)-pirrolidin-1-carboxílico (8.8 gramos, 17.9 mili-moles) y peryodinano de Dess-Martin (7.6 gramos, 17.9 mili-moles), para dar el producto del título como un aceite amarillo, el cual se utilizó en el siguiente paso sin purificación. TLC, R_f (AcOEt) = 0.55. t_R (HPLC, columna Waters Symmetry C18, 3.5 micras, 2.1 x 50 milímetros, del 20 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo HCOOH al 0.1 por ciento, flujo: 0.6 mililitros/minuto): 3.77 minutos.

D. Terbutil-éster del ácido (3R,4R)-3-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-4-metil-amino-metil-pirrolidin-1-carboxílico.

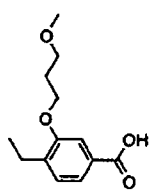
De una manera similar a la descrita en el Ejemplo 9 para el paso de reacción J, se preparan los siguientes materiales de inicio a partir del terbutil-éster del ácido (3R,4S)-3-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-4-formil-pirrolidin-1-carboxílico (3.5 gramos, 6 milimoles), metil-amina (0.93 mililitros, 30 milimoles), y $NaBH_4$ (0.454 gramos, 12 milimoles), y purificación mediante cromatografía por evaporación instantánea sobre gel de sílice (CH_2Cl_2/MeOH, 1:1) hasta (CH_2Cl_2/MeOH/NH_4OH, 89:10:1), para dar el compuesto del título como un aceite incoloro. TLC, R_f (CH_2Cl_2/MeOH/NH_4OH, 89:10:1) = 0.29. MS (LC-MS): 506.2 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por. ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.38 minutos.

E. Terbutil-éster del ácido (3R,4R)-3-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-4-[(metil-fenil-acetil-amino)-metil]-pirrolidin-1-carboxílico.

A partir del terbutil-éster del ácido (3R,4R)-3-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-4-metil-amino-metil-pirrolidin-1-carboxílico (0.7 gramos, 1.38 milimoles), cloruro de fenil-acetilo (0.22 mililitros, 1.66 milimoles), y trietil-amina

(0.21 mililitros, 2.1 milimoles) en CH_2Cl_2 (40 mililitros), y purificación mediante cromatografía por evaporación instantánea sobre gel de sílice (ciclo-hexano/AcOEt, de 1:1 a 0:1), para dar el compuesto del título como un aceite incoloro. TLC, R_f (AcOEt) = 0.30. MS (LC-MS): 624.0 $[M+H]^+$; t_R (HPLC, columna Waters Symmetry C18, del 20 al 100 por ciento de CH_3CN/H_2O/5 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 0.6 mililitros/minuto): 4.41 minutos.

Ácido 4-etil-3-(3-metoxi-propoxi)-benzoico



a. Metil-éster del ácido 4-bromo-3-hidroxi-benzoico.

A una solución del ácido 4-bromo-3-hidroxi-benzoico (preparado de acuerdo con J. Amer. Chem. Soc. 1946, 68, 574) (5 gramos, 32.8 milimoles) en MeOH (100 mili-litros), se le agrega H_2SO_4 concentrado (1 mililitro). La solución se pone a reflujo durante 14 horas, luego se concentra hasta aproximadamente 30 mililitros, y se vierte en agua. La capa acuosa se extrae con éter (50 mililitros, 4 veces), y los extractos orgánicos combinados se neutralizan con una solución acuosa saturada de $NaHCO_3$ (50 mililitros, 2 veces), se lavan con salmuera (50 mililitros), se secan sobre Na_2SO_4, se filtran, y se concentran, para dar el compuesto del título como un polvo blanco. TLC, R_f (AcOEt) = 0.9. ^{1}H-RMN

($CDCl_3$, 300 MHz): δ = 5.8 (bs, 1H), 7.45 (d, 1H), 7.55 (d, 1H), 7.7 (s, 1H) ppm.

b. Metil-éster del ácido 4-bromo-3-(3-metoxi-propoxi)-benzoico.

Una solución del metil-éster del ácido 4-bromo-3-hidroxi-benzoico (12 gramos, 51.9 milimoles), carbonato de potasio (10.77 gramos, 77.9 milimoles), y 1-yodo-3-metoxi-propano (11.42 gramos, 57.1 milimoles) en acetonitrilo (250 mililitros), se agita a reflujo durante 16 horas. El solvente se concentra bajo presión reducida, se agrega H_2O (100 mili-litros), y la capa acuosa se extrae con éter (50 mililitros, 4 veces). Los extractos orgánicos combinados se lavan con salmuera, se secan sobre sulfato de sodio anhidro, y se concentran bajo presión reducida, para proporcionar el compuesto del título, el cual se utiliza sin mayor purificación en el siguiente paso. TLC, R_f (hexano/AcOEt, 2:1) = 0.65. ^{1}H-RMN ($CDCl_3$, 300 MHz): δ = 2.12 (p, 2H), 3.38 (s, 3H), 3.63 (t, 2H), 3.9 (s, 3H), 4.2 (t, 2H), 7.5 (d, 1H), 7.55 (d, 1H), 7.55 (m, 1H), 7.6 (d, 1H) ppm.

c. Metil-éster del ácido 3-(3-metoxi-propoxi)-4-trimetil-silanil-etinil-benzoico.

A una solución agitada del metil-éster del ácido 4-bromo-3-(3-metoxi-propoxi)-benzoico (5 gramos, 16.49 mili-moles) y trimetil-silil-acetileno (2.74 mililitros, 19.8 mili-moles) en trietil-amina (60 mililitros), se le agregan Cl_2Pd $(PPh_3)_2$ (2.31 gramos,

3.29 milimoles) y CuI (0.314 gramos, 1.65 milimoles). La mezcla resultante se agita a temperatura ambiente durante 15 horas, y se concentra bajo presión reducida. El residuo crudo se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente: hexano/AcOEt, de 10:1 a 5:1), para dar el producto del título deseado como un aceite color café. ^{1}H-RMN ($CDCl_3$, 300 MHz): δ = 0.25 (s, 9H), 2.12 (p, 2H), 3.38 (s, 3H), 3.65 (t, 2H), 3.9 (s, 3H), 4.18 (t, 2H), 7.45 (d, 1H), 7.52 (s, 1H), 7.58 (d, 1H) ppm.

d. Ácido 4-etinil-3-(3-metoxi-propoxi)-benzoico.

A una solución del metil-éster del ácido 3-(3-metoxi-propoxi)-4-trimetil-silanil-etinil-benzoico (16.49 mili-moles) en MeOH (40 mililitros), se le agrega KOH (1N, 24.7 mililitros, 24.7 milimoles). La mezcla resultante se agita a temperatura ambiente durante 15 horas, y se concentra bajo presión reducida. El residuo se recupera en HCl (2N, 100 mililitros), y se extrae con AcOEt (100 mililitros, 3 veces). Los extractos orgánicos combinados se lavan con salmuera, se secan sobre sulfato de sodio anhidro, y se concentran bajo presión reducida, para proporcionar el compuesto del título como un aceite amarillo, el cual se utiliza sin mayor purificación en el siguiente paso.

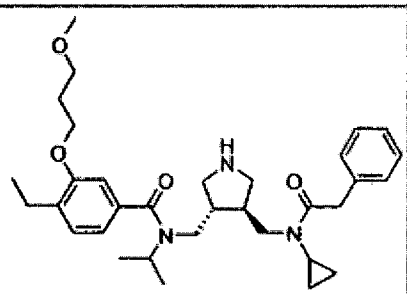
MS (FAB): 235.0 $[M+H]^+$. ^{1}H-RMN ($CDCl_3$, 300 MHz): δ = 2.15 (p, 2H), 3.38 (s, 3H), 3.41 (s, 1H), 3.62 (t, 2H), 4.22 (t, 2H), 7.5 (d, 1H), 7.65 (s, 1H), 7.68 (d, 1H) ppm.

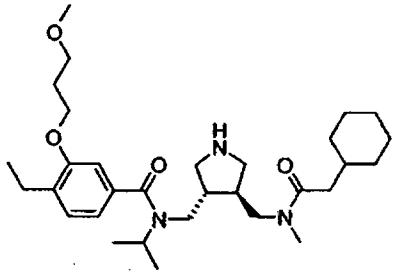
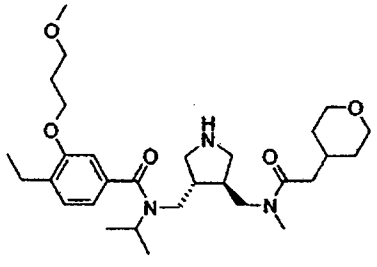
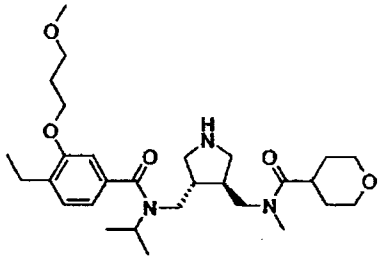
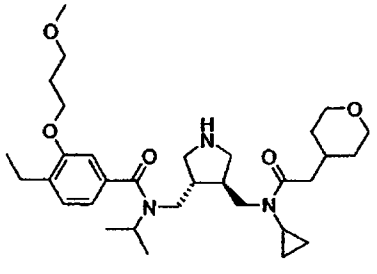
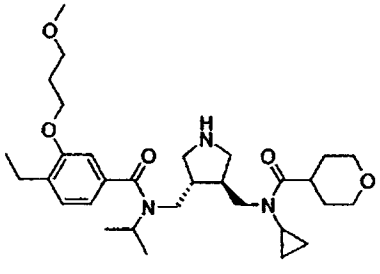
e. Ácido 4-etil-3-(3-metoxi-propoxi)-benzoico.

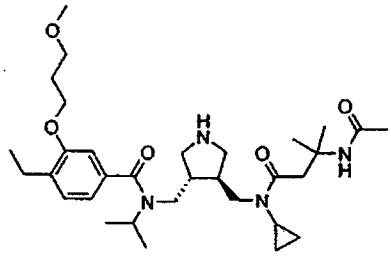
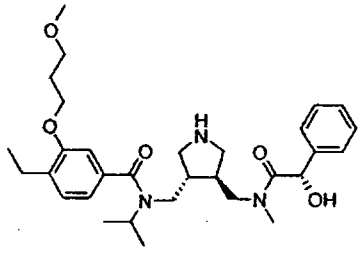
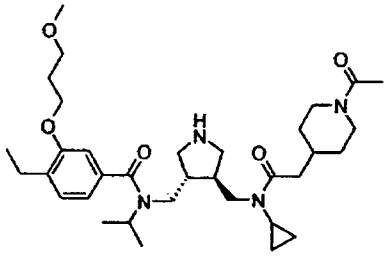
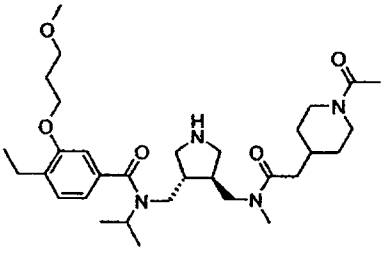
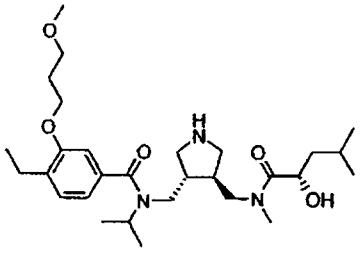
A una solución del ácido 4-etinil-3-(3-metoxi-propoxi)-benzoico (1 gramo, 4.11 milimoles) en EtOH (20 mililitros), se le agrega $Pd(OH)_2$. La mezcla resultante se agita bajo una atmósfera de hidrógeno durante 15 minutos, y luego se filtra y se concentra. El material crudo se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente: hexano/AcOEt, 2:1), para dar el compuesto del título como un polvo blanco. ^{1}H-RMN ($CDCl_3$, 300 MHz): δ = 1.2 (t, 3H), 2.15 (p, 2H), 27 (q, 2H), 3.38 (s, 3H), 3.62 (t, 2H), 4.15 (t, 2H), 7.25 (d, 1H), 7.55 (s, 1H), 7.68 (d, 1H) ppm.

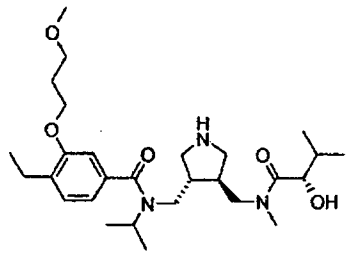
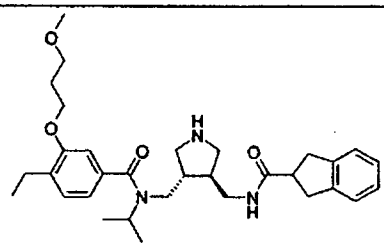
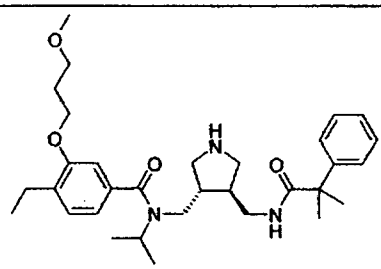
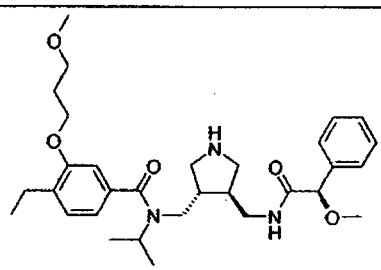
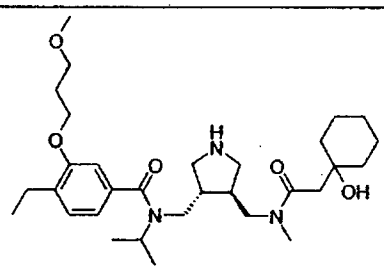
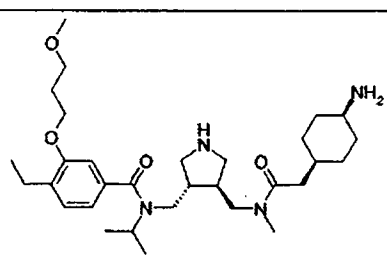
Los siguientes Ejemplos se preparan de acuerdo con los procedimientos descritos anteriormente para el Ejemplo 152:

Tabla 5

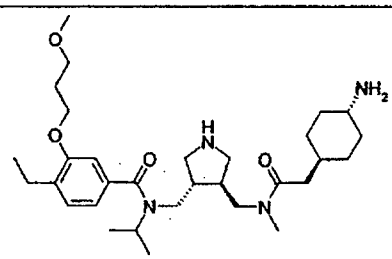
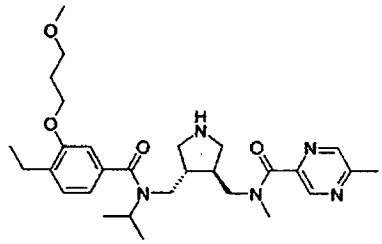
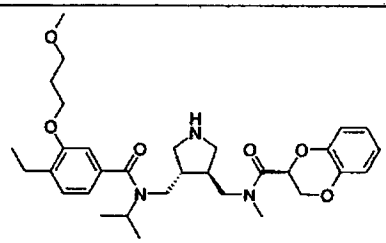
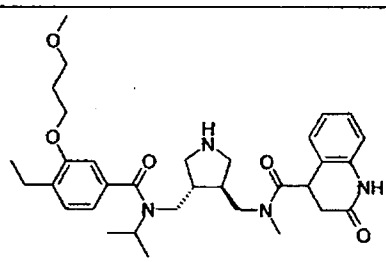
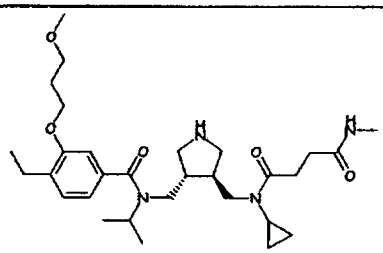
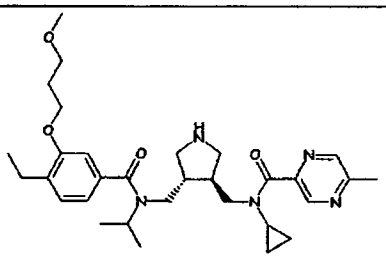
Ejemplo	Configuración	Estructura	$[M+H]^+$	t_R (HPLC)
153	(3S, 4S)		550.2	6.13[a]

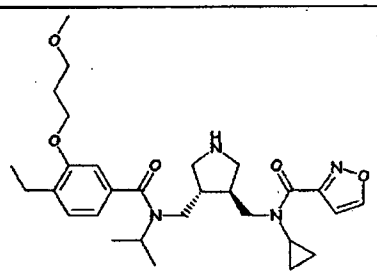
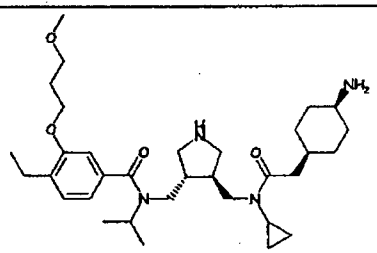
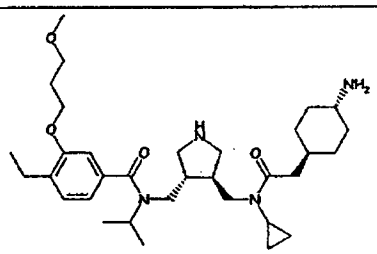
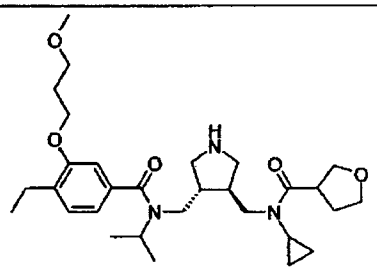
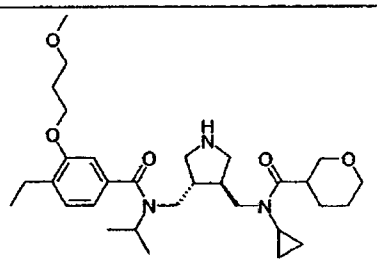
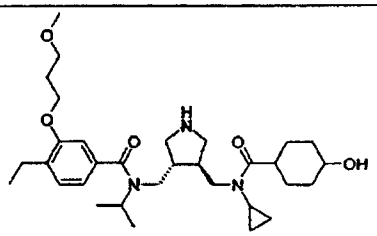
154	(3S, 4S)		530	5.55[a]
155	(3S, 4S)		532	4.10[b]
156	(3S, 4S)		518	3.97[b]
157	(3S, 4S)		558.3	4.37[b]
158	(3S, 4S)		544.3	4.25[b]

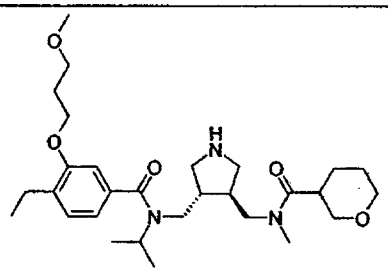
159	(3S, 4S)		573.3	2.63[c]
160	(3S, 4S)		540.3	4.88[a]
161	(3S, 4S)		599.2	2.60[c]
162	(3S, 4S)		573.2	2.20[c]
163	(3S, 4S)		520.3	2.94[d]

164	(3S, 4S)		506.4	2.86 min[d]
165	(3S,4S)		536.2	4.71[f]
166	(3S,4S)		538.2	4.76[f]
167	(3S,4S)		540.2	4.47[f]
168	(3S,4S)		546.2	4.52[f]
169	(3S,4S)		545.5	4.26[e]

590

170	(3S,4S)		545.5	4.25[e]
171	(3S,4S)		526.3	4.69[e]
172	(3S,4S)		568.2	5.24[e]
173 174	(3S,4S)		579.3 579.3	4.78[e] 4.67[e]
175	(3S,4S)		545.3	4.62[e]
176	(3S,4S)		552.3	4.86[e]

177	(3S,4S)		527.2	4.89[e]
178	(3S,4S)		571.4	4.35[e]
1791	(3S,4S)		571.4	4.41[e]
180 181	(3S,4S)		530.2	4.16[f] 4.16[f]
182 183	(3S,4S)		544.2	4.28[f] 4.32[f]
184 185	(3S,4S)		558.3	3.98[f] 4.20[f]

186 187	(3S,4S)		518.2	4.00[f] 4.04[f]

[a] t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto).

[b] t_R (Columna Nucleosil C18HD (4 x 70 milímetros, 3 micras), del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/1.5 minutos, flujo: 1 mililitro/minuto).

[c] t_R (Columna Waters Symmetry C18, del 20 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/H_2O, 2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 0.6 mililitros/minuto).

[d] t_R (Columna Waters Symmetry C18, del 5 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/H_2O, 2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 0.6 mililitros/minuto).

[e] t_R (Columna Nucleosil C18HD, del 5 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto).

[f] t_R (HPLC, columna Nucleosil C18HD, del 20 al 100 por ciento de

CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto).

Los materiales de inicio de los compuestos de título de la Tabla 5 se preparan como sigue:

Terbutil-éster del ácido (3R,4R)-3-amino-metil-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-1-carboxílico:

De acuerdo con el procedimiento descrito para el Ejemplo 130 / paso de reacción C, mediante la hidrogenación del terbutil-éster del ácido (3S,4R)-3-azidometil-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-1-carboxílico (3.95 gramos, 7.48 milimoles), disuelto en EtOH absoluto (100 mililitros), en la presencia de Pd/C al 10 por ciento (0.8 gramos; Engelhard 4505), a temperatura ambiente y bajo presión atmosférica, se proporciona, después de la filtración y del secado al vacío, el compuesto del título como un aceite incoloro. MS: 492.2 $[M+H]^+$. t_R (HPLC, columna Nucleosil C18HD, del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto): 4.62 minutos.

a. Terbutil-éster del ácido (3R,4S)-3-({[4-etil-3-(3-metoxi-

propoxi)-benzoil]-isopropil-amino}-metil)-4-metan-sulfoniloxi-metil-pirrolidin-1-carboxílico:

Se prepara a partir del terbutil-éster del ácido (3R,4S)-3-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-4-hidroxi-metil-pirrolidin-1-carboxílico (4.00 gramos, 8.12 milimoles), cloruro de metan-sulfonilo (0.733 mililitros, 9.34 milimoles), y NEt_3 (3.40 mililitros, 24.4 mili-moles) en CH_2Cl_2 (50 mililitros), de una manera similar al procedimiento descrito para el Ejemplo 130 / paso de reacción A, para dar el compuesto del título como un aceite amarillento. TLC, R_f (hexano/AcOEt, 1:3) = 0.32.

b. Terbutil-éster del ácido (3S,4R)-3-azido-metil-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-1-carboxílico:

Se prepara a partir del terbutil-éster del ácido (3R,4S)-3-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-4-metan-sulfoniloxi-metil-pirrolidin-1-carboxílico (5.50 gramos, 8.10 milimoles) y NaN_3 (2.13 gramos, 32.4 milimoles) en dimetil-formamida (40 mililitros), de una manera similar al procedimiento descrito para el Ejemplo 130 / paso de reacción B, y purificación mediante cromatografía por evaporación instantánea sobre gel de sílice (hexano/AcOEt, 1:1), para dar el compuesto del título como un aceite incoloro. TLC, R_f (hexano/AcOEt, 1:3) = 0.47. MS: 518.2 $[M+H]^+$. t_R (HPLC, columna Nucleosil C18HD, del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por

ciento, flujo: 1 mililitro/minuto): 5.89 minutos.

Terbutil-éster del ácido (3R,4R)-3-ciclopropil-amino-metil-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-4-formil-pirrolidin-1-carboxílico:

A una solución del terbutil-éster del ácido (3R,4S)-3-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-4-formil-pirrolidin-1-carboxílico (descrito en el paso C del Ejemplo 152) (6.9 gramos, 11.88 milimoles) en dicloro-etano (112 mililitros), se le agregan ciclopropil-amina (0.92 mililitros, 13.1 milimoles) y $NaBH(OAc)_3$ (3.52 gramos, 16.63 milimoles). La solución se agita a temperatura ambiente durante la noche, y luego se diluye con CH_2Cl_2. Se agrega una solución saturada de $NaHCO_3$, las capas se separan, y la acuosa se extrae dos veces con CH_2Cl_2. Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran, y se concentran al vacío. El material crudo se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente: AcOEt/MeOH, de 100:0 a 85:15), para dar el compuesto del título. MS (LC-MS): 532.3 $[M+H]^+$. t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.58 minutos.

Los materiales de inicio de los Ejemplos 173 y 174 se

preparan como sigue:

Los dos diaestereómeros de terbutil-éster del ácido (3R,4R)-3-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-4(R)-{[metil-(2-oxo-1,2,3,4-tetrahidro-quinolin-4-carbonil)amino]-metil}-pirrolidin-1-carboxílico y terbutil-éster del ácido (3R,4R)-3-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-4(S)-{[metil-2-oxo-1,2,3,4-tetrahidro-quinolin-4-carbonil)-amino]-metil}-pirrolidin-1-carboxílico, se separan mediante HPLC quiral de la mezcla diaestereoisomérica (0.5 gramos) sobre una columna Chiralcel OD (20 mM; 5 x 50 centímetros), utilizando n-hexano/EtOH/MeOH, 90:7.5:2.5, como eluyente (flujo: 90 mili-litros/minuto, detección UV a 210 nanómetros).

Los materiales de inicio de los Ejemplos 180 y 181 se preparan como sigue:

Los dos diaestereómeros de terbutil-éster del ácido (3R,4R)-3-{[ciclopropil-(tetrahidro-furan-3(R)-carbonil)-amino]-metil}-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-iso-propil-amino}-metil)-pirrolidin-1-carboxílico y terbutil-éster del ácido (3R,4R)-3-{[ciclopropil-(tetrahidro-furan-3(S)-carbonil)-amino]-metil}-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-1-carboxílico, se separan mediante HPLC quiral de la mezcla diaestereo-isomérica (0.33 gramos) sobre una columna Chiralpak AD (20 µM; 50 x 500 milímetros), utilizando n-hexano/EtOH/MeOH,

80:17.5:2.5 (velocidad de flujo: 110 mili-litros/minuto, UV 210 nanómetros).

Los materiales de inicio de los Ejemplos 182 y 183 se preparan como sigue:

Los dos diaestereómeros de terbutil-éster del ácido (3R,4R)-3-{[ciclopropil-(tetrahidro-piran-3(R)-carbonil)-amino]-metil}-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-iso-propil-amino}-metil)-pirrolidin-1-carboxílico y terbutil-éster del ácido (3R,4R)-3-{[ciclopropil-(tetrahidro-piran-3(S)-carbonil)-amino]-metil}-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-1-carboxílico, se separan mediante HPLC quiral de la mezcla diaestereo-isomérica (0.33 gramos) sobre una columna Chiralpak OD (20 µM; 50 x 500 milímetros), utilizando n-hexano/EtOH/MeOH, 97:1.5:1.5 (velocidad de flujo: 120 mili-litros/minuto, UV 210 nanómetros).

Los materiales de inicio de los Ejemplos 184 y 185 se preparan como sigue:

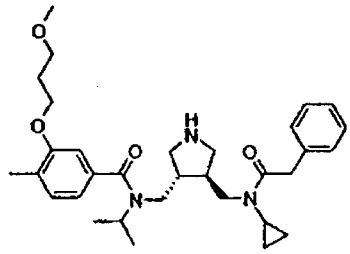
Los dos diaestereómeros de terbutil-éster del ácido (3R,4R)-3-{[ciclopropil-cis-(4-hidroxi-ciclohexan-carbonil)-amino]-metil}-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-1-carboxílico y terbutil-éster del ácido (3R,4R)-3-{[ciclopropil-trans-(4-hidroxi-ciclohexan-carbonil)-amino]-metil}-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-1-carboxílico, se separan mediante HPLC quiral de la

mezcla diaestereoisomérica (0.32 gramos) sobre una columna Chiralpak OD (20 µM; 5 x 50 centímetros), utilizando n-hexano/EtOH/MeOH, 97:1.5:1.5, como eluyente (flujo: 120 mililitros/minuto, detección UV a 210 nanómetros).

Los materiales de inicio de los Ejemplos 186 y 187 se preparan como sigue:

Los dos diaestereómeros de terbutil-éster del ácido (3R,4R)-3-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-4-{[metil-(tetrahidro-piran-3(R)-carbonil-amino]-metil}-pirrolidin-1-carboxílico y terbutil-éster del ácido (3R,4R)-3-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-4-{[metil-(tetrahidro-piran-3(S)-carbonil-amino]-metil}-pirrolidin-1-carboxílico, se separan mediante HPLC quiral de la mezcla diaestereoisomérica (0.28 gramos) sobre una columna Chiralcel AD-H (30 x 250 centímetros), utilizando un gradiente de 2-propanol/CO_2 (flujo: 130 mili-litros/minuto, detección UV a 220 nanómetros).

Ejemplo 188: N-{(3S,4S)-4-[(ciclopropil-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-N-isopropil-3-(3-metoxi-propoxi)-4-metil-benzamida



A una solución del terbutil-éster del ácido (3R,4R)-3-[(ciclopropil-fenil-acetil-amino}-metil)-pirrolidin-1-carboxílico (0.280 gramos, 0.44 milimoles) en dioxano (3 mililitros), se le agrega HCl 4N en dioxano (2.5 mililitros), y la solución resultante se liofiliza para proporcionar la sal de clorhidrato correspondiente. MS (LC-MS): 536.2 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18HD (4 x 70 milímetros, 3 micras), del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/1.5 minutos, flujo: 1 mililitro/ minuto): 4.56 minutos.

El material de inicio se prepara de una manera similar a la descrita en el Ejemplo 149, pasos de reacción A a E, como sigue:

A. Terbutil-éster del ácido (3S,4R)-3-(terbutil-dimetil-silaniloxi-metil)-4-({[4-metil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-1-carboxílico.

A partir de terbutil-éster del ácido (3S,4R)-3-(terbutil-dimetil-silaniloxi-metil)-4-(isopropil-amino-metil)-pirrolidin-1-carboxílico (5 gramos, 12.9 milimoles), ácido 4-metil-3-(3-metoxi-propoxi)-benzoico (4.06 gramos, 18.1 mili-moles), BOPCl (4.6 gramos, 18.1 milimoles), y trietil-amina (7.2 mililitros, 51.7 milimoles). TLC, R_f (AcOEt) = 0.7. MS (LC-MS): 493 $[M+H-Boc]^+$.

B. Terbutil-éster del ácido (3R,4S)-3-({[4-metil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-4-hidroxi-metil-pirrolidin-1-carboxílico.

A partir del terbutil-éster del ácido (3S,4R)-3-(terbutil-dimetil-silaniloxi-metil)-4-({[4-metil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-1-carboxílico (6.79 gramos, 11.5 milimoles) y TBAF (5.42 gramos, 17.2 milimoles), para dar el compuesto del título como un aceite amarillo, el cual se utilizó en el siguiente paso sin purificación. TLC, R_f (AcOEt) = 0.4. MS (LC-MS): 423 $[M+H-tBu]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 6.05 minutos.

C. Terbutil-éster del ácido (3R,4S)-3-({[4-metil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-4-formil-pirrolidin-1-carboxílico.

A partir del terbutil-éster del ácido (3R,4S)-3-({[4-metil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-4-hidroxi-metil-pirrolidin-1-carboxílico (5.7 gramos, 11.9 mili-moles) y peryodinano de Dess-Martin (5.1 gramos, 11.9 mili-moles), para dar el producto del título como un aceite amarillo, el cual se utiliza en el siguiente paso sin purificación. TLC, R_f (AcOEt) = 0.49.

D. Terbutil-éster del ácido (3R,4R)-3-({[4-metil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-4-ciclo-propil-amino-metil-pirrolidin-1-carboxílico.

596

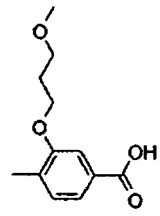
A partir del terbutil-éster del ácido (3R,4S)-3-({[4-metil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-4-formil-pirrolidin-1-carboxílico (3 gramos, 6.29 milimoles), ciclopropil-amina (0.395 mililitros, 6.92 milimoles), y $NaBHOAc_3$ (1.87 gramos, 8.81 milimoles), y purificación mediante cromatografía por evaporación instantánea sobre gel de sílice (AcOEt/MeOH, de 100:0 a 85:15), para dar el compuesto del título como un aceite incoloro. TLC, R_f (AcOEt) = 0.63. MS (LC-MS): 518.3 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18HD (4 x 70 milímetros, 3 micras), del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/1.5 minutos; flujo: 1 mililitro/minuto): 5.37 minutos.

E. Terbutil-éster del ácido (3R,4R)-3-[(ciclopropil-fenil-acetil-amino)-metil]-4-({[4-metil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-1-carboxílico.

A partir del terbutil-éster del ácido (3R,4R)-3-({[4-metil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-4-ciclopropil-amino-metil-pirrolidin-1-carboxílico (0.3 gramos, 0.579 milimoles), cloruro de fenil-acetilo (0.092 mililitros, 0.695 milimoles), y trietil-amina (0.12 mililitros, 0.869 mili-moles), y purificación mediante cromatografía por evaporación instantánea sobre gel de sílice (ciclo-hexano/ AcOEt, de 1:1 a 0:1), para dar el compuesto del título como un aceite incoloro. TLC, R_f (AcOEt/ciclo-hexano, 4:1) = 0.15. MS (LC-MS): 610.3 $[M+H]^+$; (LC-MS, columna Waters Symmetry C18, 2.1 x 30 milímetros, del 20 al 100 por ciento de

CH_3CN/H_2O/5 minutos): 4.63 minutos.

Ácido 3-(3-metoxi-propoxi)-4-metil-benzoico



a. Metil-éster del ácido 3-hidroxi-4-metil-benzoico.

A una solución del ácido 3-hidroxi-4-metil-benzoico (5 gramos, 32.8 milimoles) en MeOH (100 mililitros), se le agrega H_2SO_4 concentrado (1 mililitro). La solución se pone a reflujo durante 14 horas, luego se concentra hasta aproximadamente 30 mililitros, y se vierte en agua. La capa acuosa se extrae con éter (50 mililitros, 4 veces), y los extractos orgánicos combinados se neutralizan con una solución acuosa saturada de $NaHCO_3$ (50 mililitros, 2 veces), se lavan con salmuera (50 mililitros), se secan sobre Na_2SO_4, se filtran, y se concentran, para dar el compuesto del título como un polvo blanco. TLC, R_f (hexano/AcOEt, 2:1) = 0.55. ^{1}H-RMN ($CDCl_3$, 300 MHz): δ = 2.3 (s, 3H), 3.9 (s, 3H), 7.15 (d, 1H), 7.5 (d, 1H), 7.6 (s, 1H) ppm.

b. Metil-éster del ácido 3-(3-metoxi-propoxi)-4-metil-benzoico.

Una solución del metil-éster del ácido 3-hidroxi-4-metil-benzoico (7.7 gramos, 32.43 milimoles), carbonato de potasio (6.72 gramos, 48.65 milimoles), y 1-yodo-3-metoxi-propano (7.14 gramos, 35.68 milimoles) en acetonitrilo (125 mililitros), se agita a

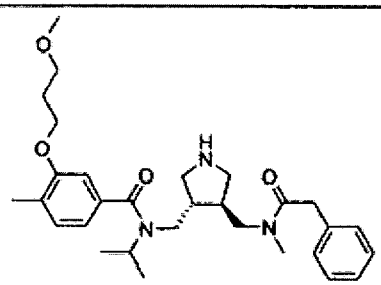
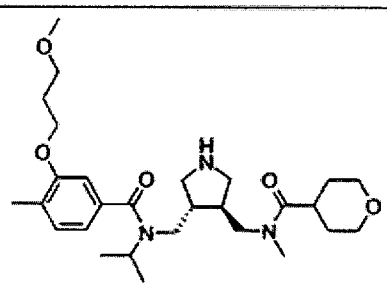
reflujo durante 26 horas. El solvente se concentra bajo presión reducida, se agrega H_2O (100 mili-litros), y la capa acuosa se extrae con éter (50 mililitros, 4 veces). Los extractos orgánicos combinados se lavan con salmuera, se secan sobre sulfato de sodio anhidro, y se concentran bajo presión reducida, para proporcionar el compuesto del título, el cual se utiliza sin mayor purificación en el siguiente paso. TLC, R_f (hexano/AcOEt, 2:1) = 0.65. ^{1}H-RMN ($CDCl_3$, 300 MHz): δ = 2.10 (p, 2H), 2.3 (s, 3H), 3.38 (s, 3H), 3.62 (t, 2H), 3.9 (s, 3H), 4.15 (t, 2H), 7.15 (d, 1H), 7.45 (s, 1H), 7.55 (d, 1H) ppm.

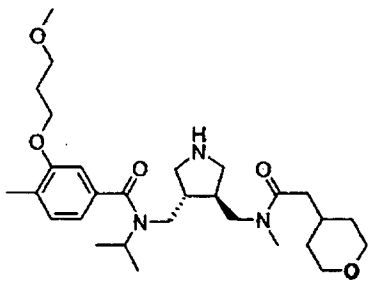
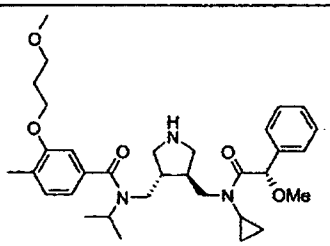
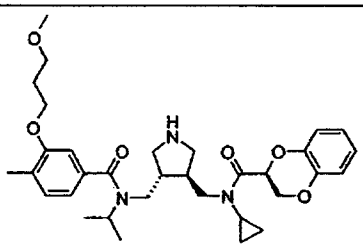
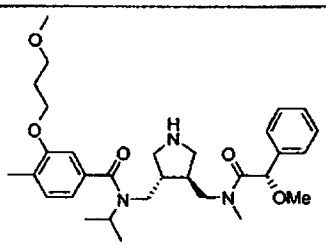
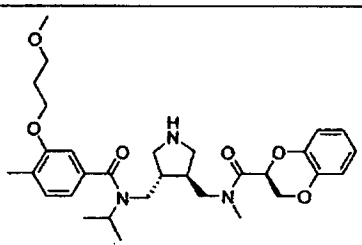
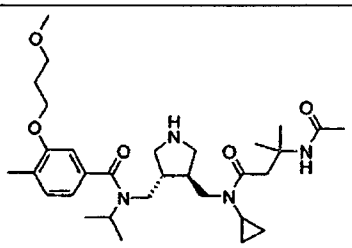
c. Ácido 3-(3-metoxi-propoxi)-4-metil-benzoico.

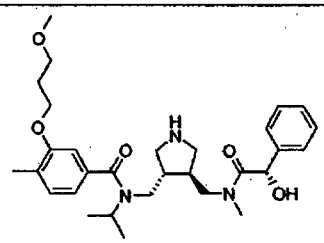
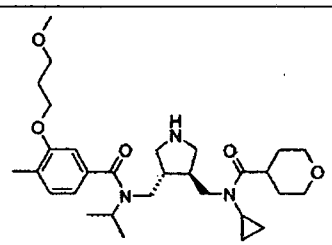
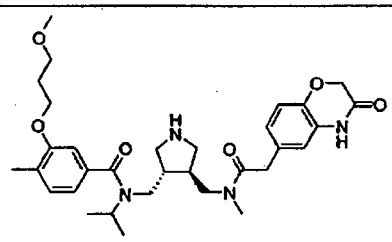
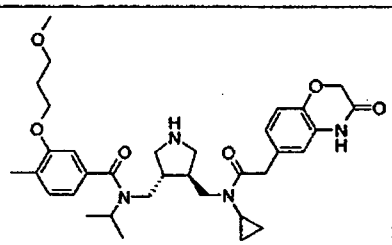
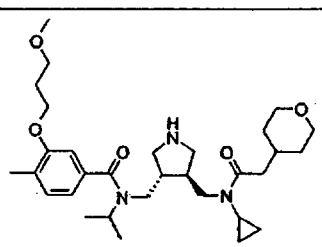
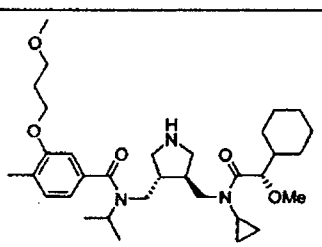
Una solución del metil-éster del ácido 3-(3-metoxi-propoxi)-4-metil-benzoico (7.12 gramos, 32.86 milimoles) y NaOH (1N en agua, 100 mililitros, 100 milimoles) en EtOH (100 mililitros), se pone a reflujo durante 1 hora. La mezcla de reacción se deja llegar a la temperatura ambiente, y el solvente se concentra bajo presión reducida. El residuo se disuelve en agua (200 mililitros), y se lava con éter (50 mili-litros, 3 veces). El pH se ajusta a 2 mediante la adición de HCl concentrado, y la capa acuosa se extrae con AcOEt (150 mililitros, 2 veces). Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran, y se concentran al vacío. El material crudo se recristaliza en dietil-éter/hexano, para proporcionar el producto del título deseado. TLC, R_f

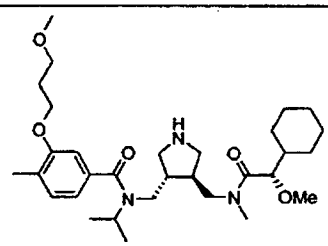
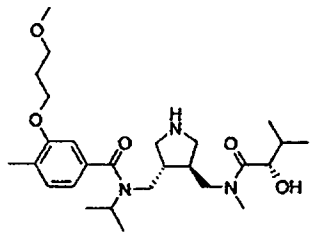
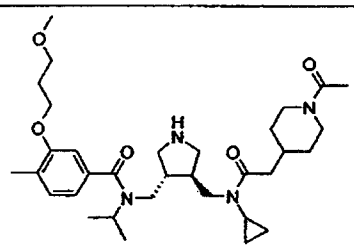
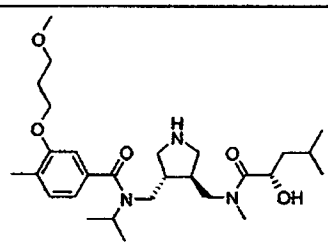
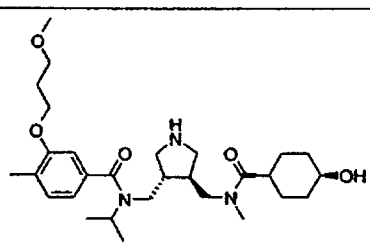
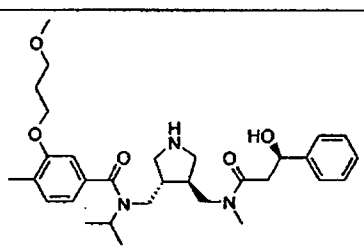
(hexano/AcOEt, 2:1) = 0.15. MS (LC-MS): 224.0 $[M+H]^+$; ^{1}H-RMN ($CDCl_3$, 300 MHz): δ = 2.10 (p, 2H), 2.3 (s, 3H), 3.38 (s, 3H), 3.62 (t, 2H), 4.15 (t, 2H), 7.2 (d, 1H), 7.55 (s, 1H), 7.65 (d, 1H) ppm.

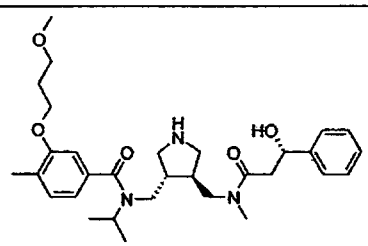
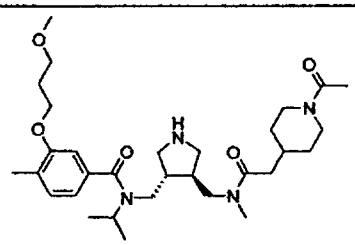
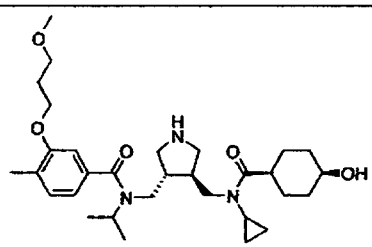
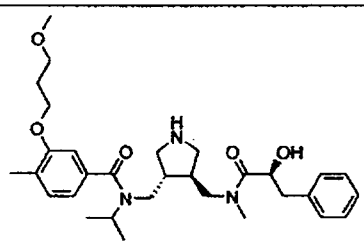
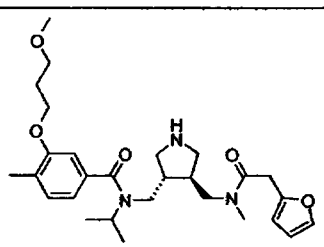
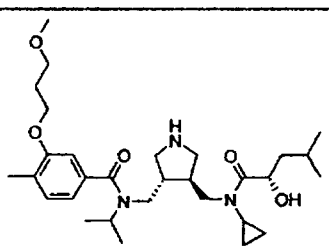
Los siguientes Ejemplos se preparan de acuerdo con los procedimientos descritos anteriormente para el Ejemplo 188:

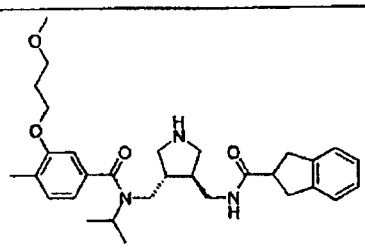
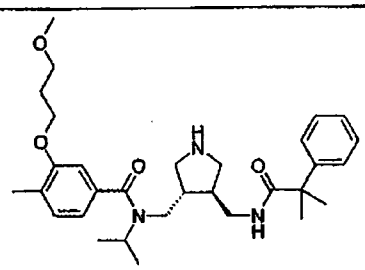
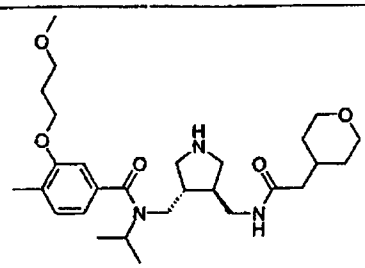
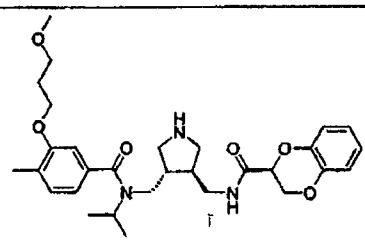
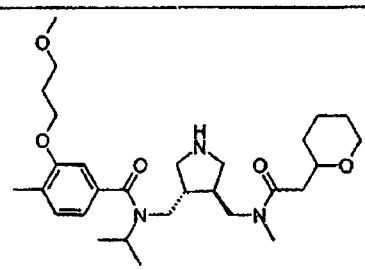
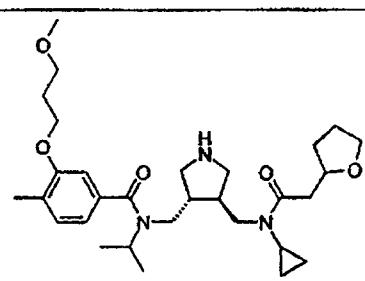
Ejemplo	Configuración	Estructura	$[M+H]^+$	t_R (HPLC)
189	(3S, 4S)		510.2	4.21[a]
190	(3S, 4S)		504.4	4.45[a]

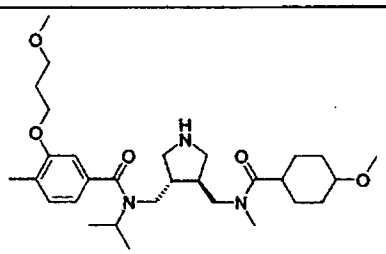
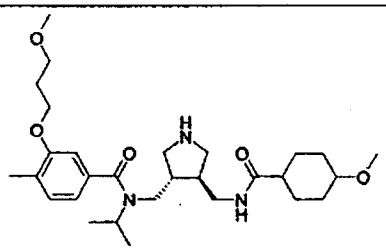
191	(3S, 4S)		518.3	4.47[a]
192	(3S, 4S)		566.2	4.92[a]
193	(3S, 4S)		580.3	5.14[a]
194	(3S, 4S)		540.3	4.81[a]
195	(3S, 4S)		554.2	4.96[a]
196	(3S, 4S)		559.3	4.69[a]

197	(3S, 4S)		526.3	4.71[a]
198	(3S, 4S)		530.3	4.64[a]
199	(3S, 4S)		581.2	2.45[b]
200	(3S, 4S)		607.2	2.60[b]
201	(3S, 4S)		544.2	2.30[b]
202	(3S, 4S)		572.3	3.05[c]

203	(3S, 4S)		546.3	3.02[c]
204	(3S, 4S)		492.3	2.46[b]
205	(3S, 4S)		585.3	2.47[b]
206	(3S, 4S)		506.4	2.82[c]
207	(3S, 4S)		518.3	2.67[c]
208	(3S, 4S)		540.3	2.57[b]

209	(3S, 4S)		540.3	2.61[b]
210	(3S, 4S)		559.2	1.87[b]
211	(3S, 4S)		544.3	2.79[c]
212	(3S, 4S)		540.3	2.66[b]
213	(3S, 4S)		500.2	2.52[b]
214	(3S, 4S)		532.3	2.89[c]

215	(3S,4S)		522.2	4.45[e]
216	(3S,4S)		524.2	4.53[e]
217	(3S,4S)		504.2	3.53[e]
218	(3S,4S)		540.2	4.94[d]
219 220	(3S,4S)		518.3	3.97e 3.99e
221 222	(3S,4S)		530.2	4.07[e] 4.09[e]

223 224	(3S,4S)		532.2	3.92[e] 4.08[e]
225 226	(3S,4S)		518.2	3.76[e] 3.90[e]

[a] t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto).

[b] t_R (Columna Waters Symmetry C18, del 20 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/H_2O, 2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 0.6 mililitros/minuto).

[c] t_R (Columna Waters Symmetry C18, del 5 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/H_2O, 2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 0.6 mililitros/minuto).

[d] t_R (HPLC, columna Nucleosil C18HD, del 5 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto).

[e] t_R (HPLC, columna Nucleosil C18HD, del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto).

Los materiales de inicio de los compuestos de título de la Tabla 6, se preparan como sigue:

Terbutil-éster del ácido (3R,4R)-3-amino-metil-4-({iso-propil-[3-(3-metoxi-propoxi)-4-metil-benzoil]-amino}-metil)-pirrolidin-1-carboxílico:

De acuerdo con el procedimiento descrito para el Ejemplo 130 / paso de reacción C, mediante la hidrogenación del terbutil-éster del ácido (3S,4R)-3-azido-metil-4-({iso-propil-[3-(3-metoxi-propoxi)-4-metil-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (3.68 gramos, 7.31 milimoles), disuelto en MeOH (80 mililitros), en la presencia de Pd/C al 10 por ciento (1.0 gramos; Engelhard 4505), a temperatura ambiente y bajo presión atmosférica, para dar, después de la filtración y del secado al vacío, el compuesto del título como un aceite. MS: 478.2 $[M+H]^+$. t_R (HPLC, columna Nucleosil C18HD, del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto): 4.28 minutos.

a. Terbutil-éster del ácido (3R,4S)-3-({isopropil-[3-(3-metoxi-propoxi)-4-metil-benzoil]-amino}-metil)-4-metan-sulfoniloxi-metil-pirrolidin-1-carboxílico:

Se prepara a partir del terbutil-éster del ácido (3S,4R)-3-hidroxi-metil-4-({isopropil-[3-(3-metoxi-propoxi)-4-metil-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (3.80 gramos, 7.94 milimoles), cloruro de metansulfonilo (0.717 mililitros, 9.13 milimoles), y NEt_3 (3.32 mililitros, 23.8 mili-moles) en CH_2Cl_2 (50 mililitros), de una manera similar al procedimiento descrito para el Ejemplo 130 / paso de reacción A, para dar el compuesto del título como un aceite amarillento. TLC, R_f (hexano/AcOEt, 1:3) = 0.21.

b. Terbutil-éster del ácido (3S,4R)-3-azidometil-4-({isopropil-[3-(3-metoxi-propoxi)-4-metil-benzoil]-amino}-metil)-pirrolidin-1-carboxílico:

Se prepara a partir del terbutil-éster del ácido (3R,4S)-3-({isopropil-[3-(3-metoxi-propoxi)-4-metil-benzoil]-amino}-metil)-4-metan-sulfoniloxi-metil-pirrolidin-1-carboxílico (4.42 gramos, 7.94 milimoles) y NaN_3 (2.09 gramos, 31.8 milimoles) en dimetil-formamida (40 mililitros), de una manera similar al procedimiento descrito para el Ejemplo 130 / paso de reacción B, y purificación mediante cromatografía por evaporación instantánea sobre gel de sílice (hexano/AcOEt, 1:1), para dar el compuesto del título como un aceite. TLC, R_f (hexano/AcOEt, 1:3) = 0.45. MS: 504.2 $[M+H]^+$. t_R (HPLC, columna Nucleosil C18HD, del 20 al 100 por ciento de

CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto): 5.65 minutos.

Terbutil-éster del ácido (3R,4R)-3-({[4-metil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-4-metil-amino-metil-pirrolidin-1-carboxílico

De una manera similar a la descrita en el Ejemplo 9 para el paso de reacción J, se preparan los siguientes materiales de inicio a partir del terbutil-éster del ácido (3R,4S)-3-({[4-metil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-4-formil-pirrolidin-1-carboxílico (preparado según C del Ejemplo 190) (2 gramos, 4.2 milimoles), una solución 2N de metil-amina en MeOH (10.5 mililitros, 21 mili-moles) y $NaBH_4$ (0.318 gramos, 8.40 milimoles), y purificación mediante cromatografía por evaporación instantánea sobre gel de sílice (AcOEt/MeOH, 90:10, luego AcOEt/MeOH/NH_4OH, 89:10:1), para dar un aceite incoloro. MS: 492.1 $[M+H]^+$.

Los materiales de inicio de los Ejemplos 219 y 220, se preparan como sigue:

Los dos diaestereómeros de terbutil-éster del ácido (3R,4R)-3-({isopropil-[3-(3-metoxi-propoxi)-4-metil-benzoil]-amino}-metil)-4-{[metil-(2-tetrahidro-piran-2(R)-il-acetil)-amino]-metil}-pirrolidin-1-carboxílico y terbutil-éster del ácido (3R,4R)-3-

({isopropil-[3-(3-metoxi-propoxi)-4-metil-benzoil]-amino}-metil)-4-{[metil-(2-tetrahidro-piran-2(S)-il-acetil)-amino]-metil}-pirrolidin-1-carboxílico, se separan mediante HPLC quiral de la mezcla diaestereoisomérica (0.59 gramos) sobre una columna Chiralpak AD (20 µM; 5 x 50 centímetros), utilizando n-hexano/isopropanol, 8:2, conteniendo ácido trifluoroacético al 0.1 por ciento, como eluyente (flujo de 100 mililitros/minuto, detección UV a 210 nanómetros).

Los materiales de inicio de los Ejemplos 221 y 222 se preparan como sigue:

Los dos diaestereómeros de terbutil-éster del ácido (3R,4R)-3-{[ciclopropil-[2-tetrahidro-furan-2(R)-il-acetil)-amino]-metil}-4-({isopropil-[3-(3-metoxi-propoxi)-4-metil-benzoil]-amino}-metil)-pirrolidin-1-carboxílico y terbutil-éster del ácido (3R,4R)-3-{[ciclopropil-(2-tetrahidro-furan-2(S)-il-acetil)-amino]-metil}-4-({isopropil-[3-(3-metoxi-propoxi)-4-metil-benzoil]-amino}-metil)-pirrolidin-1-carboxílico, se separan mediante HPLC quiral de la mezcla diaestereo-isomérica (0.33 gramos) sobre una columna Chiralpak AD (20 µM; 5 x 50 centímetros), utilizando n-hexano/EtOH/MeOH, 80:15:15 como eluyente (flujo de 120 mililitros/minuto, detección UV a 210 nanómetros).

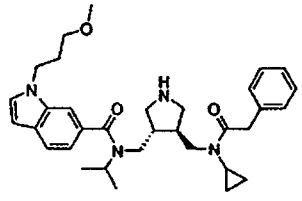
Los materiales de inicio de los Ejemplos 223 y 224 se preparan como sigue:

Los dos diaestereómeros de terbutil-éster del ácido (3R,4R)-3-({isopropil-[3-(3-metoxi-propoxi)-4-metil-benzoil]-amino}-metil)-4-{[cis-(4-metoxi-ciclohexan-carbonil)-metil-amino]-metil}-pirrolidin-1-carboxílico y terbutil-éster del ácido (3R,4R)-3-({isopropil-[3-(3-metoxi-propoxi)-4-metil-benzoil]-amino}-metil)-4-{[trans-(4-metoxi-ciclohexan-carbonil)-metil-amino]-metil}-pirrolidin-1-carboxílico, se separan mediante HPLC quiral de la mezcla diaestereo-isomérica (0.50 gramos) sobre una columna Chiralpak OD (20 µM; 5 x 50 centímetros), utilizando n-hexano/EtOH/MeOH, 97:1.5:1.5 como eluyente (flujo de 120 mililitros/minuto, detección UV a 210 nanómetros).

Los materiales de inicio de los Ejemplos 225 y 226 se preparan como sigue:

Los dos diaestereómeros de terbutil-éster del ácido (3R,4R)-3-({isopropil-[3-(3-metoxi-propoxi)-4-metil-benzoil]-amino}-metil)-4-{[cis-(4-metoxi-ciclohexan-carbonil)-amino]-metil}-pirrolidin-1-carboxílico y terbutil-éster del ácido (3R,4R)-3-({isopropil-[3-(3-metoxi-propoxi)-4-metil-benzoil]-amino}-metil)-4-{[trans-(4-metoxi-ciclohexan-carbonil)-amino]-metil}-pirrolidin-1-carboxílico, se separan mediante HPLC quiral de la mezcla diaestereoisomérica (0.29 gramos) sobre una columna Chiralpak OD (20 µM; 5 x 50 centímetros), utilizando n-hexano/EtOH/MeOH, 97:1.5:1.5 como eluyente (flujo de 120 mililitros/minuto, detección UV a 210 nanómetros).

Ejemplo 227: {(3S,4S)-4-[(ciclopropil-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-isopropil-amida del ácido 1-(3-metoxi-propil)-1H-indol-6-carboxílico



A una solución del terbutil-éster del ácido (3R,4R)-3-[(ciclopropil-fenil-acetil-amino)-metil]-4-({isopropil-[1-(3-metoxi-propil)-1H-indol-6-carbonil]-amino}-metil)-pirrolidin-1-carboxílico (0.15 gramos, 0.232 milimoles) en dioxano (3 mililitros), se le agrega HCl 4N en dioxano (1 mililitro), y la solución resultante se liofiliza para proporcionar la sal de clorhidrato correspondiente. MS (LC-MS): 545.2 $[M+H]^+$. t_R (HPLC, columna Waters Symmetry C18, 3.5 micras, 2.1 x 50 milímetros, del 20 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo HCOOH al 0.1 por ciento, flujo: 0.6 mililitros/ minuto): 2.46 minutos.

El material de inicio se prepara de una manera similar a la descrita en el Ejemplo 149, pasos de reacción A a E, como sigue:

A. Terbutil-éster del ácido (3S,4R)-3-(terbutil-dimetil-silaniloxi-metil)-4-({isopropil-[1-(3-metoxi-propil)-1H-indol-6-carbonil]-amino}-metil)-pirrolidin-1-carboxílico.

A partir de terbutil-éster del ácido (3S,4R)-3-(ter-butil-dimetil-silaniloxi-metil)-4-(isopropil-amino-metil)-pirrolidin-1-carboxílico (5 gramos, 12.9 milimoles), ácido 1-(3-metoxi-propil)-1H-indol-6-carboxílico (4.22 gramos, 18.1 milimoles), BOPCl (4.6 gramos, 18.1 milimoles), y trietil-amina (7.2 mililitros, 51.7 milimoles). TLC, R_f (AcOEt) = 0.32.

B. Terbutil-éster del ácido (3S,4R)-3-hidroxi-metil-4-({isopropil-[1-(3-metoxi-propil)-1H-indol-6-carbonil]-amino}-metil)-pirrolidin-1-carboxílico.

A partir del terbutil-éster del ácido (3S,4R)-3-(ter-butil-dimetil-silaniloxi-metil)-4-({isopropil-[1-(3-metoxi-propil)-1H-indol-6-carbonil]-amino}-metil)-pirrolidin-1-carboxílico (6.79 gramos, 11.3 milimoles) y TBAF (5.35 gramos, 17.0 milimoles), y purificación mediante cromatografía por evaporación instantánea sobre gel de sílice (ciclo-hexano/AcOEt, de 50:50 a 0:100 hasta AcOEt/MeOH, 90:10). TLC, R_f (AcOEt) = 0.34. MS (LC-MS): 432 $[M+H-tBu]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.73 minutos.

C. Terbutil-éster del ácido (3S,4R)-3-formil-4-({iso-propil-[1-(3-metoxi-propil)-1H-indol-6-carbonil]-amino}-metil)-pirrolidin-1-carboxílico.

A partir del terbutil-éster del ácido (3S,4R)-3-hidroxi-metil-4-({isopropil-[1-(3-metoxi-propil)-1H-indol-6-carbonil]-amino}-metil)-pirrolidin-1-carboxílico (4.3 gramos, 8.82 milimoles) y peryodinano de Dess-Martin (4.11 gramos, 9.70 milimoles), para dar el producto del título como un aceite amarillo, el cual se utiliza en el siguiente paso sin purificación.

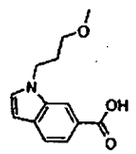
D. Terbutil-éster del ácido (3R4R)-3-ciclopropil-amino-metil-4-({isopropil-[1-(3-metoxi-propil)-1H-indol-6-carbonil]-amino}-metil)-pirrolidin-1-carboxílico.

A partir del terbutil-éster del ácido (3S,4R)-3-formil-4-({isopropil-[1-(3-metoxi-propil)-1H-indol-6-carbonil]-amino}-metil)-pirrolidin-1-carboxílico (2 gramos, 4.12 mili-moles), ciclopropil-amina (0.318 mililitros, 4.53 milimoles), y $NaBHOAc_3$ (1.2 gramos, 5.77 milimoles), y purificación mediante cromatografía por evaporación instantánea sobre gel de sílice (CH_2Cl_2/MeOH, 95:5, hasta CH_2Cl_2/MeOH/NH_4OH, 90:10:1). MS (LC-MS): 527.3 $[M+H]^+$; t_R (Columna Waters Symmetry C18, 3.5 micras, 2.1 x 50 milímetros, del 20 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo HCOOH al 0.1 por ciento, flujo: 0.6 mililitros/minuto): 2.45 minutos.

E. Terbutil-éster del ácido (3R,4R)-3-[(ciclopropil-fenil-acetil-amino)-metil]-4-({isopropil-[1-(3-metoxi-propil)-1H-indol-6-carbonil]-amino}-metil)-pirrolidin-1-carboxílico.

A partir del terbutil-éster del ácido (3R,4R)-3-ciclo-propil-amino-metil-4-({isopropil-[1-(3-metoxi-propil)-1H-indol-6-carbonil]-amino}-metil)-pirrolidin-1-carboxílico (0.25 gramos, 0.475 milimoles), cloruro de fenil-acetilo (0.069 mili-litros, 0.522 milimoles), y trietil-amina (0.079 mililitros, 0.569 milimoles), y purificación mediante HPLC de preparación (C18-ODB-5 micras, 19 x 50 milímetros, eluyente: CH_3CN/H_2O + HCOOH al 0.1 por ciento). MS (LC-MS): 645.3 $[M+H]^+$; t_R (HPLC, columna Waters Symmetry C18, 3.5 micras, 2.1 x 50 milímetros, del 20 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo HCOOH al 0.1 por ciento, flujo: 0.6 mililitros/minuto): 4.11 minutos.

Ácido 1-(3-metoxi-propil)-1H-indol-6-carboxílico



a. Metil-éster del ácido 1-(3-metoxi-propil)-1H-indol-6-carboxílico.

A una solución de indol-6-carboxilato de metilo (5.0 gramos, 28.5 milimoles) en dimetil-formamida (25 mililitros), se le agrega bajo nitrógeno, una dispersión de NaH al 60 por ciento en aceite (1.25 gramos, 31.3 milimoles); la mezcla se calienta a 60°C durante 2 horas, se enfría a temperatura ambiente, y se agrega 1-bromo-3-metoxi-propano (8.7 gramos, 57.0 milimoles). La mezcla

se agita adicionalmente a 60°C durante la noche. La mezcla cruda se vierte en una solución acuosa de NH_4Cl, y se diluye con CH_2Cl_2. Las capas se separan, y la acuosa se extrae dos veces con CH_2Cl_2. Los extractos orgánicos combinados se lavan con agua, se secan sobre Na_2SO_4, se filtran, y se concentran, para dar el producto del título. MS (LC-MS): 248.0 $[M+H]^+$. t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.69 minutos.

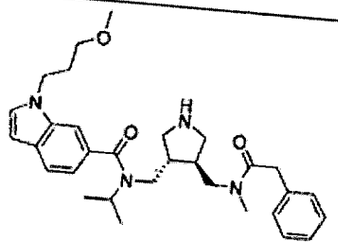
b. Ácido 1-(3-metoxi-propil)-1H-indol-6-carboxílico.

A una solución del metil-éster del ácido 1-(3-metoxi-propil)-1H-indol-6-carboxílico (7 gramos, 28.5 milimoles) en MeOH (50 mililitros), se le agrega NaOH 2N (28.5 mililitros), y la mezcla se agita durante 3 horas. El solvente se concentra, y el residuo acuoso restante se acidifica con HCl 1N, y se extrae dos veces con CH_2Cl_2. Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran, y se concentran para dar el producto del título. TLC, R_f (ciclo-hexano/AcOEt, 2:1) = 0.25. MS (LC-MS): 232.0 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, flujo: 1.5 mililitros/minuto): 5.04 minutos.

El siguiente Ejemplo se prepara de acuerdo con los

procedimientos descritos anteriormente para el Ejemplo 227:

Tabla 7

Ejemplo	Configuración	Estructura	$[M+H]^+$	t_R (HPLC)
228	(3S, 4S)		519.3	2.32

t_R (HPLC, columna Waters Symmetry C18, 3.5 micras, 2.1 x 50 milímetros, del 20 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo HCOOH al 0.1 por ciento, flujo: 0.6 mililitros/minuto).

El material de inicio del compuesto del título de la Tabla 7 se prepara como sigue:

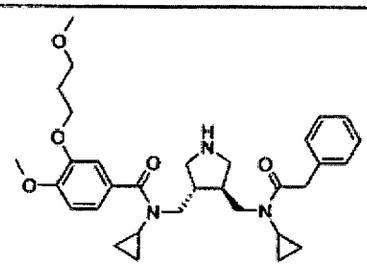
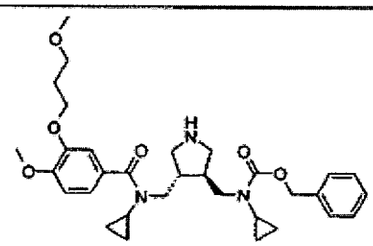
Terbutil-éster del ácido (3R,4R)-3-({isopropil-[1-(3-metoxi-propil)-1H-indol-6-carbonil]-amino}-metil)-4-metil-amino-metil-pirrolidin-1-carboxílico

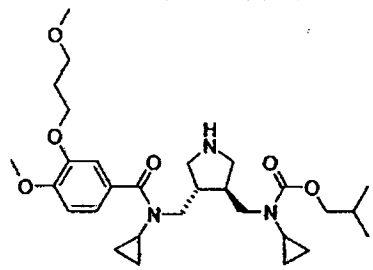
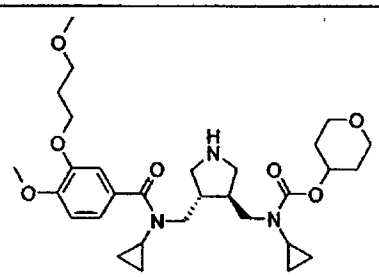
De una manera similar a la descrita en el Ejemplo 9 para el paso de reacción J, se prepara el siguiente material de inicio a partir del terbutil-éster del ácido (3S,4R)-3-formil-4-({isopropil-[1-(3-metoxi-propil)-1H-indol-6-carbonil]-amino}-metil)-pirrolidin-1-carboxílico (2 gramos, 4.12 mili-moles) (preparado según C del Ejemplo 229), una solución 2N de metil-amina en MeOH (10.3

mililitros, 20.6 milimoles), y $NaBH_4$ (0.156 gramos, 4.12 milimoles), y purificación mediante cromatografía por evaporación instantánea sobre gel de sílice (CH_2Cl_2/MeOH, 95:5, hasta CH_2Cl_2/MeOH/NH_4OH, 90:10:1). MS (LC-MS): 501.3 $[M+H]^+$; t_R (Columna Waters Symmetry C18, 3.5 micras, 2.1 x 50 milímetros, del 20 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo HCOOH al 0.1 por ciento, flujo: 0.6 mililitros/minuto): 2.40 minutos.

Los siguientes Ejemplos se preparan de acuerdo con los procedimientos descritos anteriormente para los Ejemplos 227, 233, y 282, utilizando el terbutil-éster del ácido (3R,4R)-3-ciclopropil-amino-metil-4-({ciclopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico:

Tabla 8

Ejemplo	Configuración	Estructura	$[M+H]^+$	t_R (HPLC)
229	(3S, 4S)		550	3.86
230	(3S, 4S)		565.9	5.16

231	(3S, 4S)		532	5.23
232	(3S, 4S)		560.2	3.33

t_R (HPLC, columna Nucleosil C18HD, del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/1.5 minutos, flujo: 1 mililitro/minuto).

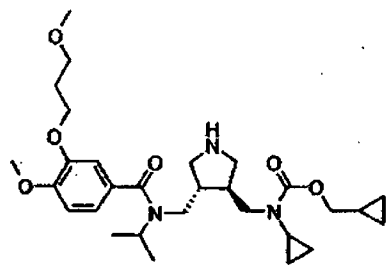
El material de inicio de los compuestos de título de la Tabla 8 se prepara como sigue:

Terbutil-éster del ácido (3R,4R)-3-ciclopropil-amino-metil-4-({ciclopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico

De una manera similar a la descrita en el Ejemplo 149 para el paso de reacción D, se prepara el siguiente material de inicio a partir del terbutil-éster del ácido (3R,4S)-3-({ciclopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-4-formil-pirrolidin-1-

carboxílico (1.79 gramos, 3.65 milimoles) (preparado de acuerdo con el Ejemplo 9, utilizando ciclopropil-amina en lugar de isopropil-amina según F), ciclopropil-amina (0.287 mililitros, 4.01 mili-moles), y $NaBHOAc_3$ (1.14 gramos, 5.11 milimoles), para dar el compuesto del título, el cual se utiliza en los siguientes pasos sin mayor purificación. TLC, R_f (CH_2Cl_2/AcOEt, 9:1) = 0.35. MS (LC-MS): 532.0 $[M+H]^+$.

Ejemplo 233: Ciclopropil-metil-éster del ácido ciclopropil-[(3S*,4S*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico



A una solución del terbutil-éster del ácido (3S*,4R*)-3-[(ciclopropil-ciclopropil-metoxi-carbonil-amino)-metil]-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (140 miligramos, 0.222 milimoles) en dioxano (4 mililitros), se le agrega HCl 4N en dioxano (2 mililitros), y la solución resultante se agita a temperatura ambiente durante 7 horas. La liofilización proporciona la sal de clorhidrato correspondiente. MS (LC-MS): 532.1 $[M+H]^+$; t_R (HPLC, columna

Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.37 minutos.

El material de inicio se prepara como sigue:

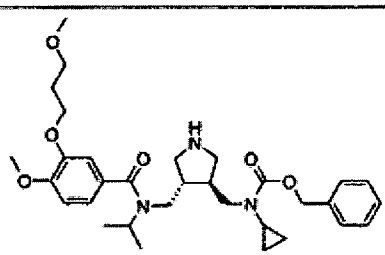
Terbutil-éster del ácido (3S*,4R*)-3-[(ciclopropil-ciclopropil-metoxi-carbonil-amino)-metil]-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico.

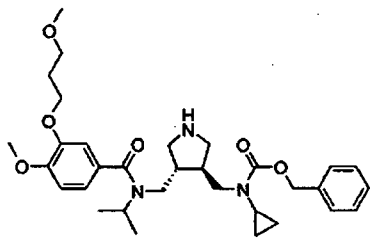
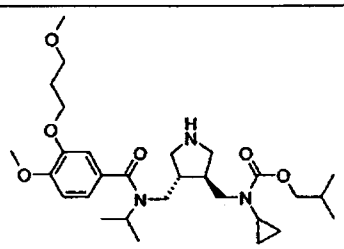
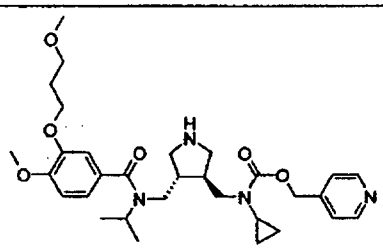
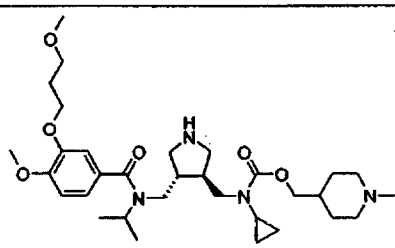
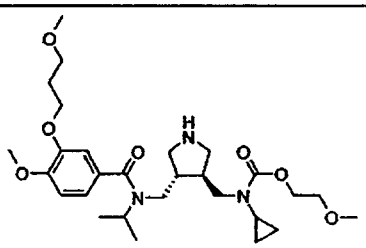
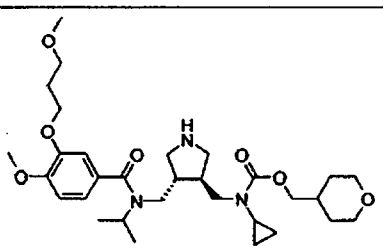
A una solución de ciclopropil-metanol (29 micro-litros, 0.366 milimoles) en CH_2Cl_2 (5 mililitros), se le agregan carbonato de bis-(tricloro-metilo) (40 miligramos, 0.136 mili-moles), seguido por DMAP (143 miligramos, 1.170 milimoles), y la suspensión lechosa resultante se agita a temperatura ambiente durante 15 minutos. Entonces se agrega una solución de terbutil-éster del ácido ((3R*,4R*)-3-ciclopropil-amino-metil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (215 miligramos, 0.403 milimoles) en CH_2Cl_2 (5 mililitros), y la solución transparente resultante se agita a temperatura ambiente durante otras 3.5 horas. La evaporación del solvente proporciona el producto crudo, el cual se purifica mediante HPLC de preparación (Waters C_{18} ODB, eluyente: H_2O/CH_3CN, del 20 al 100 por ciento), para dar el compuesto del título. MS (LC-MS): 532.0 $[M+H-Boc]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100

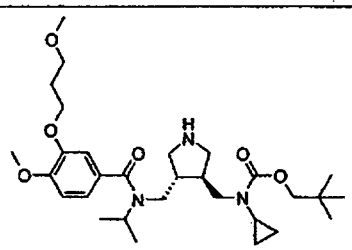
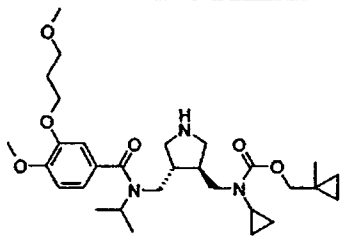
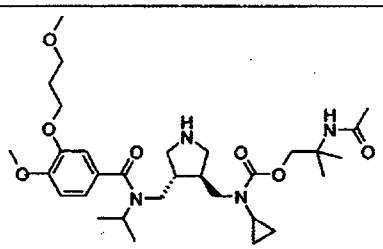
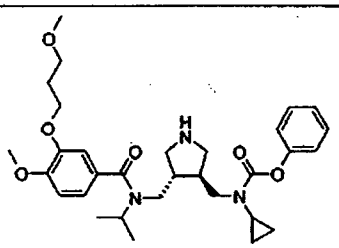
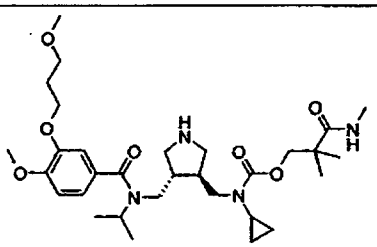
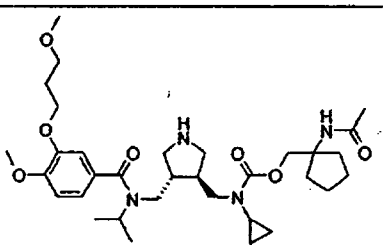
por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 6.48 minutos.

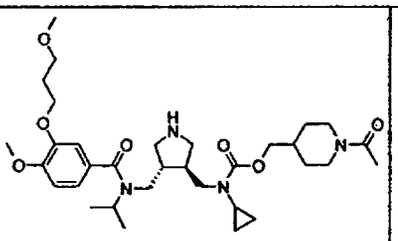
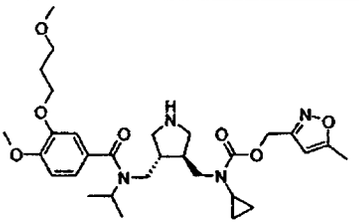
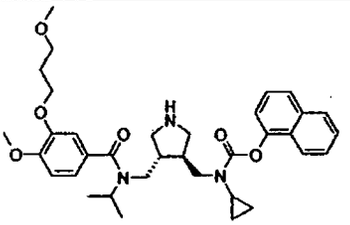
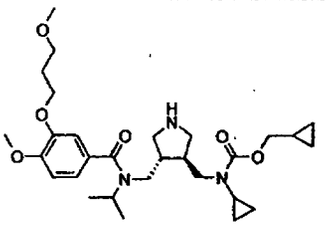
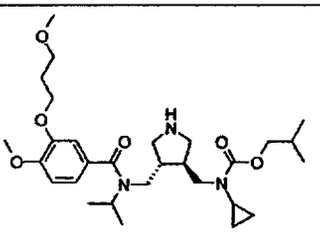
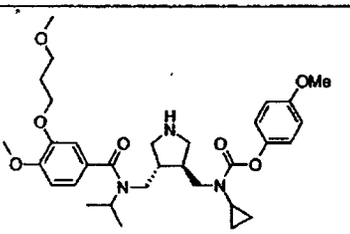
Los siguientes ejemplos se preparan de acuerdo con los procedimientos descritos anteriormente para el Ejemplo 233, o como se describe más adelante para el Ejemplo 282:

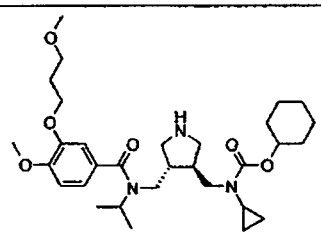
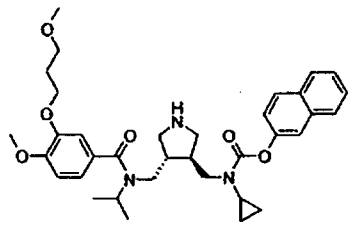
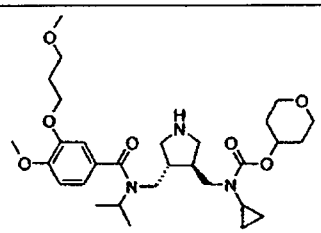
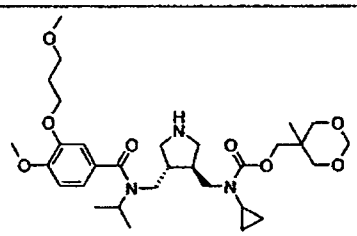
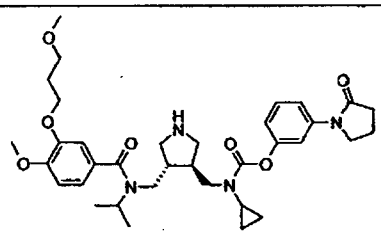
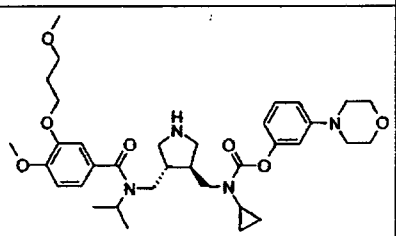
Tabla 9

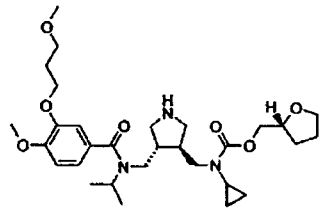
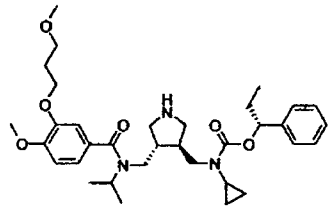
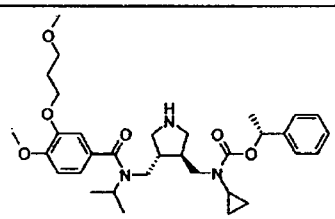
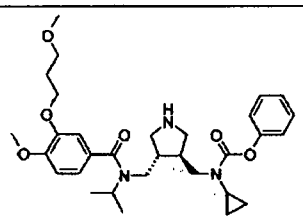
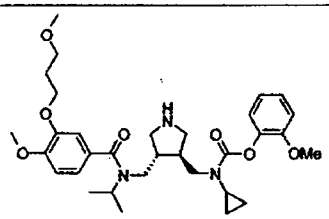
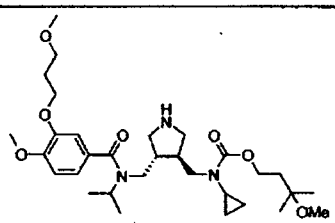
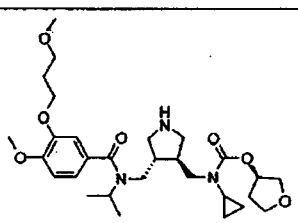
Ejemplo	Configuración	Estructura	$[M+H]^+$	t_R (HPLC)
234	(3S*, 4S*)		568.0	5.27[a]

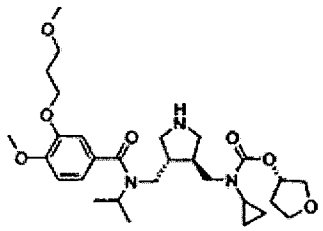
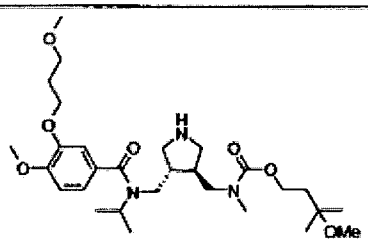
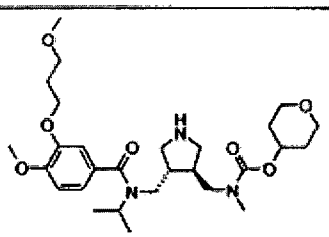
235	(3S, 4S)		568.2	5.17[a]
236	(3S*, 4S*)		534.1	5.35[a]
237	(3S*, 4S*)		285.1 $[M+2H]^{2+}$	4.70[a]
238	(3S*, 4S*)		295.1 $[M+2H]^{2+}$	4.72[a]
239	(3S*, 4S*)		536.0	5.10[a]
240	(3S*, 4S*)		576.1	5.25[a]

241	(3S*, 4S*)		548.1	5.83[a]
242	(3S*, 4S*)		546.1	4.76[a]
243	(3S*, 4S*)		591.4	4.25[a]
244	(3S*, 4S*)		554.3	4.70[a]
245	(3S*, 4S*)		591.4	4.19[a]
246	(3S*, 4S*)		617.4	4.41[a]

247	(3S*, 4S*)		617.5	4.26[a]
248	(3S*, 4S*)		573.4	4.54[a]
249	(3S*, 4S*)		604.2	5.14[a]
250	(3S, 4S)		532.3	4.87[a]
251	(3S, 4S)		534.2	5.11[a]
252	(3S, 4S)		584.2	5.69[a]

253	(3S, 4S)		560.2	5.92[a]
254	(3S, 4S)		604.2	6.01[a]
255	(3S, 4S)		562.3	5.42[a]
256	(3S, 4S)		592.3	5.58[a]
257	(3S, 4S)		637.5	5.88[a]
258	(3S, 4S)		639.2	5.90[a]

259	(3S, 4S)		562.5	5.41[a]
260	(3S, 4S)		596.0	6.35[a]
261	(3S, 4S)		582.0	5.03[a]
262	(3S, 4S)		554.0	4.83[a]
263	(3S, 4S)		584.0	4.85[a]
264	(3S, 4S)		578.5	3.36[b]
265	(3S, 4S)		548.5	3.08[b]

266	(3S, 4S)		548.4	0.38[b]
267	(3S, 4S)		552.2	4.44[a]
268	(3S, 4S)		536.2	2.58[c]

[a] t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto).

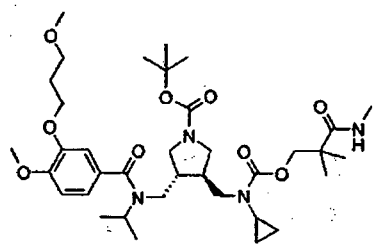
[b] t_R (Columna Waters Symmetry C18, del 10 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/H_2O, 2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 0.6 mililitros/minuto).

[c] t_R (Columna Waters Symmetry C18, del 5 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/H_2O, 2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 0.6 mililitros/minuto).

2027

El material de inicio del Ejemplo 245 se prepara como sigue:

Terbutil-éster del ácido (3S*,4R*)-3-{[ciclopropil-(2-metil-2-metil-carbamoil-propoxi-carbonil)-amino]-metil}-4-({iso-propil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico.



Se agrega HBTU (161 miligramos, 0.43 milimoles) a una solución del terbutil-éster del ácido (3S*,4R*)-3-{[(2-carboxi-2-metil-propoxi-carbonil)-ciclopropil-amino]-metil}-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (240 miligramos, 0.35 mili-moles) en CH_3CN (10 mililitros) a 0°C. Después de 5 minutos, se agrega una solución de metil-amina (44 microlitros, 0.35 milimoles, 8M en EtOH) y trietil-amina (493 microlitros, 3.54 milimoles) en CH_3CN (10 mililitros), a 0°C, y la solución de la reacción se agita a temperatura ambiente durante 5 horas. Se agrega otra porción de metil-amina (0.22 mililitros, 1.75 mili-moles), y se continúa la agitación durante otras 16 horas. Luego se agregan trietil-amina (247 microlitros, 1.77 mili-moles) y HBTU (268 miligramos, 1.02 milimoles), y la mezcla de reacción se agita a 50°C durante otras 16 horas. El solvente se

evapora, y el producto crudo se purifica mediante HPLC (Interchrom C_{18} ODB, 10 micras, 28 x 250 milímetros, eluyente: CH_2CN/H_2O al 5 por ciento/2.5 minutos, CH_2CN/H_2O del 5 al 100 por ciento/23 minutos, 100 por ciento de CH_3CN/ 4.5 minutos, flujo de 40 mililitros/minuto), para dar el compuesto del título. MS (LC-MS): 691.4 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.38 minutos.

El material de inicio se prepara como sigue:

A. Terbutil-éster del ácido (3S*,4R*)-3-{[ciclopropil-(2-metoxi-carbonil-2-metil-propoxi-carbonil)-amino]-metil}-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico.

El compuesto del título se prepara de una manera análoga a la descrita anteriormente para NVP-BGW706 a partir del terbutil-éster del ácido ((3R*,4R*)-3-ciclopropil-amino-metil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico y 2,2-dimetil-3-hidroxi-propionato de metilo, utilizando carbonato de bis-(tricloro-metilo). MS (LC-MS): 592.1 $[M+H-Boc]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por

ciento, flujo: 1.5 mililitros/minuto): 5.92 minutos.

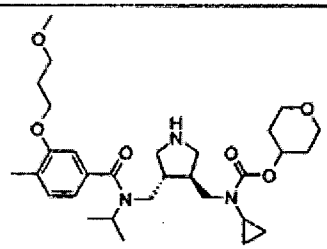
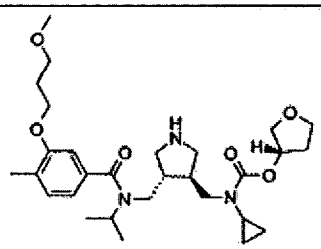
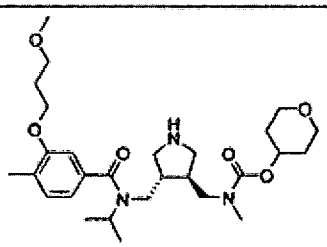
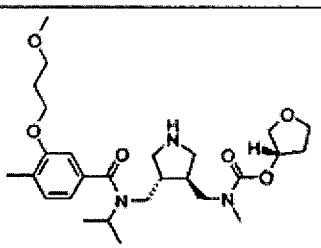
B. Terbutil-éster del ácido (3S*,4R*)-3-{[(2-carboxi-2-metil-propoxi-carbonil)-ciclopropil-amino]-metil}-4-({iso-propil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico.

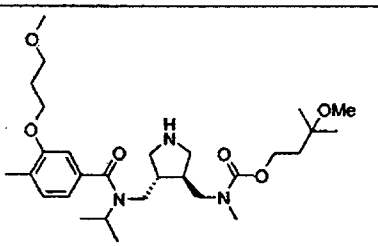
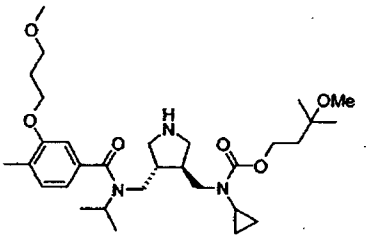
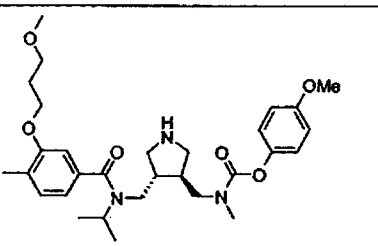
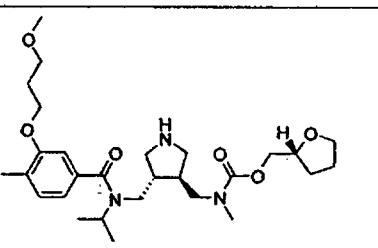
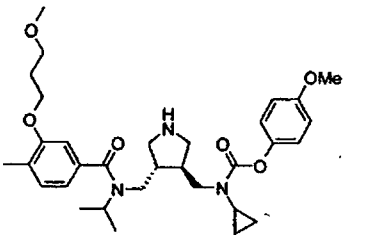
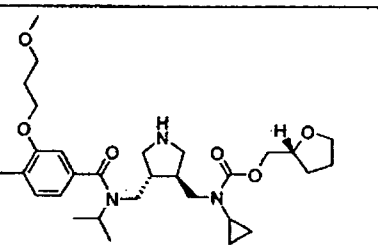
Una mezcla del terbutil-éster del ácido (3S*,4R*)-3-{[ciclopropil-(2-metoxi-carbonil-2-metil-propoxi-carbonil)-amino]-metil}-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (290 mili-gramos, 0.42 milimoles) y $LiOH \cdot H_2O$ (44 miligramos, 1.05 milimoles) en H_2O (2 mililitros) y tetrahidrofurano (6 mili-litros), se agita a temperatura ambiente durante 3 días. Después de la evaporación del solvente, se agrega HCl 1N, y la mezcla se extrae con acetato de etilo. El secado (Na_2SO_4) de los extractos combinados, la filtración, y la evaporación del solvente, proporcionan el compuesto del título, el cual se utiliza sin mayor purificación. MS (LC-MS): 578.0 $[M+H-Boc]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.44 minutos.

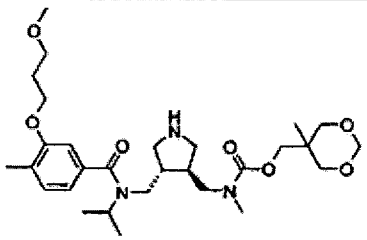
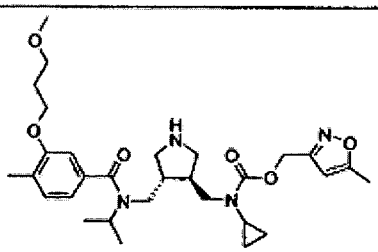
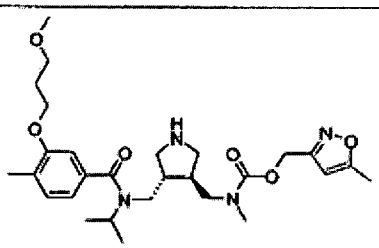
Los siguientes Ejemplos se preparan de acuerdo con los procedimientos descritos anteriormente para el Ejemplo 233 o más adelante para el Ejemplo 282, utilizando el terbutil-éster del ácido (3R,4R)-3-ciclopropil-amino-metil-4-({isopropil-[3-(3-metoxi-propoxi)-4-metil-benzoil]-amino}-metil)-pirrolidin-1-carboxílico o el

terbutil-éster del ácido (3R,4R)-3-({isopropil-[3-(3-metoxi-propoxi)-4-metil-benzoil]-amino}-metil)-4-metil-amino-metil-pirrolidin-1-carboxílico:

Tabla 10

Ejemplo	Configuración	Estructura	$[M+H]^+$	t_R (HPLC)
269	(3S, 4S)		546.3	5.76[a]
270	(3S, 4S)		532.3	4.71[a]
271	(3S, 4S)		520.3	4.57[a]
272	(3S, 4S)		506.2	4.52[a]

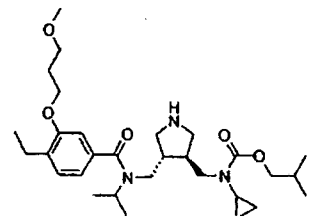
273	(3S, 4S)		536.3	2.64[b]
274	(3S, 4S)		562.3	5.03[a]
275	(3S, 4S)		542.2	5.00[a]
276	(3S, 4S)		520.3	4.67[a]
277	(3S, 4S)		568.3	5.18[a]
278	(3S, 4S)		546.3	4.85[a]

279	(3S, 4S)		550.3	4.74[a]
280	(3S, 4S)		557.2	2.68[b]
281	(3S, 4S)		531.1	2.51[b]

[a] t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto).

[b] t_R (Columna Waters Symmetry C18, del 20 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/H_2O, 2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 0.6 mililitros/minuto).

Ejemplo 282: Isobutil-éster del ácido ciclopropil-[(3S,4S)-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-3-ilmetil]-carbámico



A una solución del terbutil-éster del ácido (3S,4R)-3-[(ciclopropil-isobutoxi-carbonil-amino)-metil]-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-1-carboxílico (0.280 gramos, 0.443 milimoles) en dioxano (2 mililitros), se le agrega HCl 4N en dioxano (2 mililitros), y la solución resultante se liofiliza para proporcionar la sal de clorhidrato correspondiente. MS (LC-MS): 532 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.52 minutos.

El material de inicio se prepara como sigue:

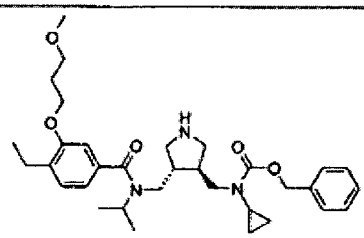
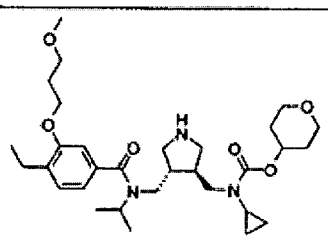
Terbutil-éster del ácido (3S,4R)-3-[(ciclopropil-isobutoxi-carbonil-amino)-metil]-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-1-carboxílico.

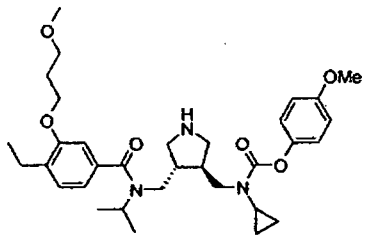
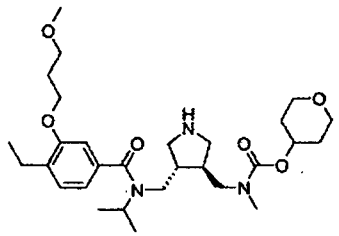
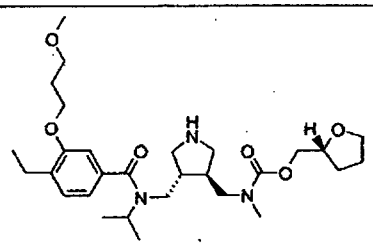
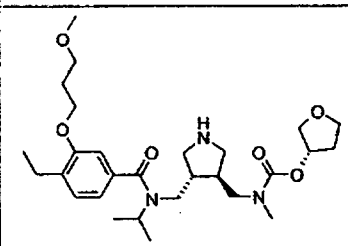
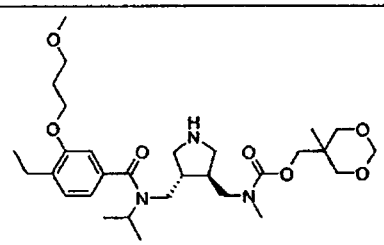
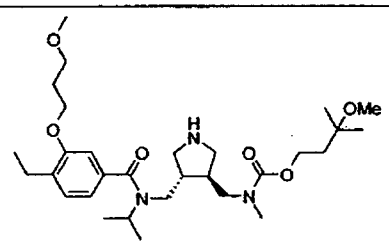
A una solución del terbutil-éster del ácido (3R,4R)-3-ciclopropil-amino-metil-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-1-carboxílico (250 miligramos, 0.470 milimoles) en CH_2Cl_2 (3 mililitros), se le agregan cloroformato de isobutilo (84 miligramos, 0.611 mili-moles) y trietil-amina (85 microlitros, 0.611 milimoles) bajo una atmósfera

de N_2. La mezcla se agita durante la noche a temperatura ambiente, se diluye con CH_2Cl_2, y se vierte en una solución acuosa saturada de $NaHCO_3$. Las capas se separan, y la acuosa se extrae dos veces con CH_2Cl_2. Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran, y se concentran. El residuo crudo se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente: CH_2Cl_2/MeOH, de 100:0 a 90:10), para dar el compuesto del título. MS (LC-MS): 532 $[M+H\text{-}Boc]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 8.22 minutos.

Los siguientes Ejemplos se preparan de acuerdo con los procedimientos descritos anteriormente para el Ejemplo 233 o el Ejemplo 282:

Tabla 11

Ejemplo	Configuración	Estructura	$[M+H]^+$	t_R (HPLC)
283	(3S, 4S)		556	5.53[a]
284	(3S, 4S)		560.3	2.68[b]

285	(3S, 4S)		582.2	2.95[b]
286	(3S, 4S)		534.2	4.80[a]
287	(3S, 4S)		534.2	4.87[a]
288	(3S, 4S)		520.3	4.73[a]
289	(3S, 4S)		564.3	4.91[a]
290	(3S, 4S)		550.2	2.80[b]

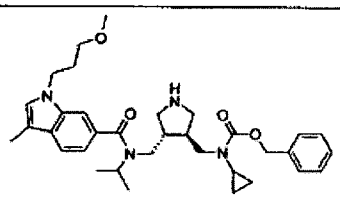
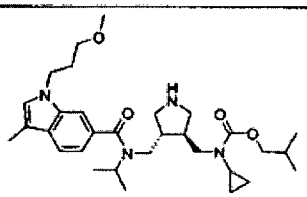
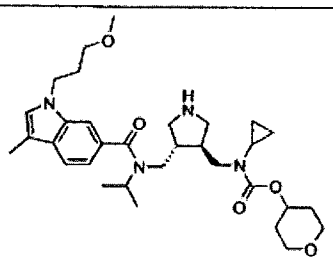
[a] t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al

100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto).

[b] t_R (Columna Waters Symmetry C18, del 20 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/H_2O, 2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 0.6 mililitros/minuto).

Los siguientes Ejemplos se preparan de acuerdo con los procedimientos descritos anteriormente para el Ejemplo 233 o el Ejemplo 282, utilizando el terbutil-éster del ácido (3R,4R)-3-ciclopropil-amino-metil-4-({isopropil-[1-(3-metoxi-propil)-3-metil-1H-indol-6-carbonil]-amino}-metil)-pirrolidin-1-carboxílico.

Tabla 12

Ejemplo	Configuración	Estructura	$[M+H]^+$	t_R (HPLC)
291	(3S, 4S)		575	5.67[a]
292	(3S, 4S)		541	5.66[a]
293	(3S, 4S)		569.3	4.22[b]

[a] t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto).

[b] t_R (Columna Nucleosil C-18HD (4 x 70 milímetros, 3 micras), del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/1.5 minutos, flujo: 1 mililitro/ minuto).

N-(2-hidroxi-1,1-dimetil-etil)-acetamida

Una mezcla de 2-amino-2-metil-propan-1-ol (2.0 mililitros, 20.4 milimoles), acetanhídrido (1.9 mililitros, 20.4 milimoles), y $NaHCO_3$ (2.6 gramos, 30.6 milimoles) en H_2O (20 mililitros), se agita a temperatura ambiente durante 16 horas. Para el procesamiento, se agrega HCl 1N, y la mezcla se extrae con acetato de etilo. El secado (Na_2SO_4) de los extractos combinados, la filtración, y la evaporación del solvente, producen el compuesto del título como un sólido incoloro. MS (LC-MS): $[M+H]^+$ = 132.2. t_R (HPLC, columna Waters Symmetry C18, del 20 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/H_2O, 2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 0.6 mililitros/minuto): 0.38 minutos.

N-(1-hidroxi-metil-ciclopentil)-acetamida

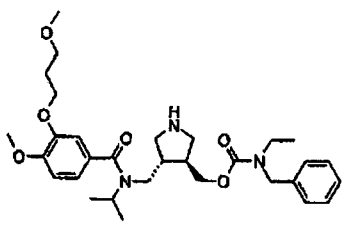
El compuesto del título se prepara de una manera análoga a la descrita para la N-(2-hidroxi-1,1-dimetil-etil)-acetamida a partir de (1-amino-ciclopentil)-metanol. MS (LC-MS): $[M+H]^+$ = 158.2. t_R

(HPLC, columna Waters SunFire C18, del 5 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/H_2O, 2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 0.8 mililitros/ minuto): 1.76 minutos.

1-(4-hidroxi-metil-piperidin-1-il)-etanona

El compuesto del título se prepara de una manera análoga a la descrita para la N-(2-hidroxi-1,1-dimetil-etil)-acetamida a partir de piperidin-4-il-metanol. MS (LC-MS): $[M+H]^+$ = 158.3. t_R (HPLC, columna Waters Symmetry C18, del 5 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/H_2O, 2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 0.6 mililitros/minuto): 0.39 minutos.

Ejemplo 294: (3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil-pirrolidin-3-ilmetil-éster del ácido bencil-etil-carbámico



A una solución del terbutil-éster del ácido (3S,4R)-3-[(bencil-etil-carbamoiloxi)-metil]-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (83 miligramos, 0.127 milimoles) en 2 mililitros de dioxano, se le agrega HCl 4N en dioxano (1 mililitro, 4 mili-moles). La mezcla se

agita a temperatura ambiente durante 2 horas, y la solución resultante se liofiliza para proporcionar la sal de clorhidrato correspondiente. MS (LC-MS): 556.1 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 4.89 minutos.

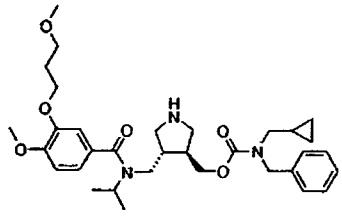
El material de inicio se prepara como sigue:

Terbutil-éster del ácido (3S,4R)-3-[(bencil-etil-carbamoil-oxi)-metil]-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico.

A una solución agitada del terbutil-éster del ácido (3S,4R)-3-hidroxi-metil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (250 miligramos, 0.505 milimoles) en CH_2Cl_2 (10 mililitros), se le agrega trifosgeno (56 miligramos, 0.187 milimoles) y DMAP (197 miligramos, 1.62 milimoles). La solución resultante se agita durante 30 minutos antes de la adición de la N-etil-bencil-amina comercialmente disponible (113 microlitros, 0.758 milimoles). La mezcla se agita adicionalmente durante la noche, luego se diluye con CH_2Cl_2, y se vierte en una solución acuosa saturada de $NaHCO_3$. Las capas se separan, y la acuosa se extrae dos veces con CH_2Cl_2. Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran, y se concentran. El material crudo se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice

(eluyente: CH_2Cl_2/MeOH, de 100:0 a 98:2). TLC, R_f (CH_2Cl_2/MeOH, 95:5) = 0.2. MS (LC-MS): 655.9 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 6.36 minutos.

Ejemplo 295: (3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil-éster del ácido bencil-ciclopropil-metil-carbámico



El compuesto del título se prepara de una manera análoga a la descrita en el Ejemplo 294, a partir del terbutil-éster del ácido (3S,4R)-3-hidroxi-metil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico y bencil-ciclopropil-metil-amina. MS (LC-MS): 582.0 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/ minuto): 5.15 minutos.

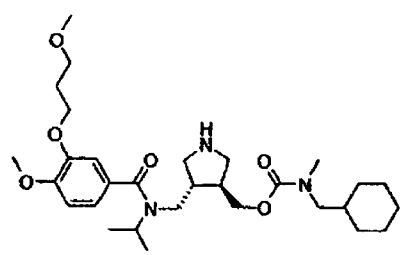
El material de inicio se prepara como sigue:

Bencil-ciclopropil-metil-amina.

Una mezcla de benzaldehído (3 mililitros, 39.55 milimoles),

ciclopropan-metil-amina (2.53 mililitros, 29.55 milimoles), AcOH (1.7 mililitros, 29.55 milimoles) en 1,2-di-cloro-etano (150 mililitros), se agita a temperatura ambiente durante 25 minutos. Se agrega triacetoxi-borohidruro de sodio (8.8 gramos, 41.37 milimoles), y la mezcla se agita adicionalmente durante la noche a temperatura ambiente. Nuevamente se agrega triacetoxi-borohidruro de sodio (3.13 gramos, 15 milimoles) para terminar la reacción. La mezcla se apaga mediante la adición de NaOH 1N (50 mililitros), las capas se separan, y la fase acuosa se extrae dos veces con éter. El material crudo se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente: CH_2Cl_2/MeOH, de 95:5 a 80:20 + NH_3 al 5 por ciento), para dar el producto del título. t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 4.91 minutos.

Ejemplo 296: (3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-il-metil-éster del ácido ciclohexil-metil-metil-carbámico



A una solución del terbutil-éster del ácido (3S,4R)-3-[(ciclohexil-metil-metil-carbamoiloxi)-metil]-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (182 miligramos, 0.281 milimoles) en 1 mililitro de dioxano, se le agrega HCl 4N en dioxano (2 mililitros, 8 milimoles). La mezcla se agita a temperatura ambiente durante 2 horas, y la solución resultante se liofiliza para proporcionar la sal de clorhidrato correspondiente. MS (LC-MS): 548 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.14 minutos.

El material de inicio se prepara como sigue:

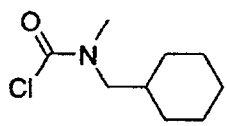
Terbutil-éster del ácido (3S,4R)-3-[(ciclohexil-metil-metil-carbamoiloxi)-metil]-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico.

A una suspensión agitada de NaH (dispersión al 60 por ciento en aceite, 17 miligramos, 0.42 milimoles) en tetrahidrofurano (2 mililitros), se le agrega, a 0°C, terbutil-éster del ácido (3S,4R)-3-hidroxi-metil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (160 miligramos, 0.303 milimoles) en tetrahidrofurano (3 mili-litros). La solución resultante se agita durante 30 minutos antes de la adición de una solución de cloruro de ciclohexil-metil-metil-carbamoílo (80 miligramos, 0.421 milimoles) en tetrahidrofurano (3 mililitros). La

mezcla se agita adicionalmente durante la noche a temperatura ambiente, y se vierte en una solución acuosa de NH_4Cl. Se agrega AcOEt, las capas se separan, y la acuosa se extrae dos veces con AcOEt. Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran, y se concentran. El material crudo se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente: CH_2Cl_2/MeOH, de 100:0 a 95:5). TLC, R_f (CH_2Cl_2/MeOH, 95:5) = 0.25. MS (LC-MS): 648 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 6.83 minutos.

Los intermediarios se preparan como se describe, mediante los siguientes métodos:

Cloruro de ciclohexil-metil-metil-carbamoílo



a. Ciclohexil-metil-metil-amina.

Una solución de ciclohexan-carbaldehído (4 mili-litros, 33.24 milimoles) y metil-amina (50.0 mililitros, 99.8 milimoles) en MeOH (160 mililitros, conteniendo AcOH al 2 por ciento), se agita a temperatura ambiente durante 1 hora. Se agrega en porciones borohidruro de sodio (2.515 gramos, 66.48 milimoles) a 0°C, y se continúa la agitación a temperatura ambiente durante 1 hora. Se

agrega una solución de NaOH, y se concentra el metanol. Se agrega CH_2Cl_2, las capas se separan, y la acuosa se extrae dos veces con CH_2Cl_2. Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran, y se concentran. El material crudo se purifica mediante cromatografía por evaporación instantánea (eluyente: CH_2Cl_2/MeOH, de 95:5 a 80:20 + NH_3 al 5 por ciento), para dar el producto del título. TLC, R_f (CH_2Cl_2/MeOH, 95:5) = 0.1. t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, flujo: 1.5 mililitros/minuto): 7.09 minutos.

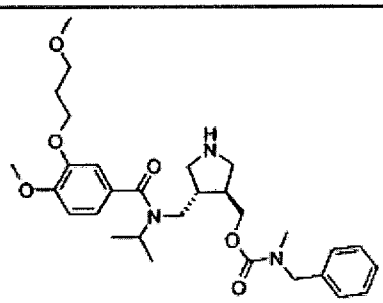
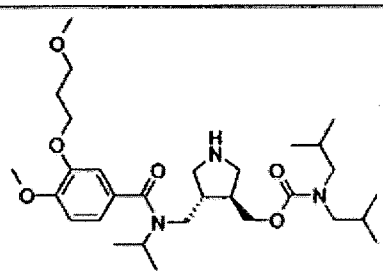
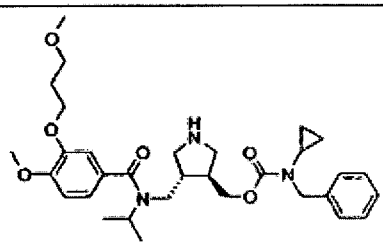
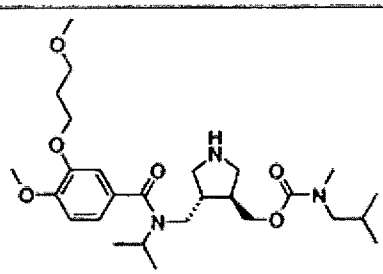
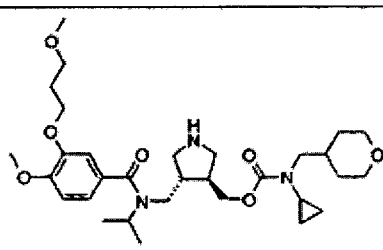
b. Cloruro de ciclohexil-metil-metil-carbamoílo.

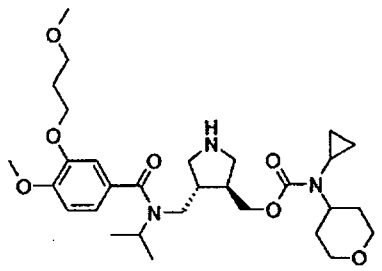
A una solución de trifosgeno (77 miligramos, 0.259 milimoles) en CH_2Cl_2 (1 mililitro) a -78°C, se le agrega por goteo piridina (63 microlitros, 0.786 milimoles), seguido por una solución de ciclohexil-metil-metil-amina (100 miligramos, 0.786 milimoles) en CH_2Cl_2 (1 mililitro). La mezcla amarilla se deja llegar a la temperatura ambiente, y se agita durante la noche. El solvente se concentra, y el residuo se recupera en AcOEt. Se agrega una solución acuosa saturada de $NaHCO_3$, las capas se separan, y la acuosa se extrae dos veces con AcOEt. Los extractos orgánicos combinados se lavan con salmuera, se secan sobre Na_2SO_4, se filtran, y se concentran, para proporcionar el compuesto del título como un aceite amarillo. TLC, R_f (CH_2Cl_2/MeOH, 95:5) = 0.95. MS (LC-MS): 189.1 $[M+H]^+$.

Los siguientes Ejemplos se preparan de acuerdo con los

procedimientos descritos anteriormente para el Ejemplo 296:

Tabla 13

Ejemplo	Configuración	Estructura	[M+H]$^+$	t_R (HPLC)
297	(3S*, 4S*)		542.5	4.70[a]
298	(3S, 4S)		550	5.33[a]
299	(3S, 4S)		568	4.15[a]
300	(3S, 4S)		508	5.13[a]
301	(3S, 4S)		576.3	4.44[a]

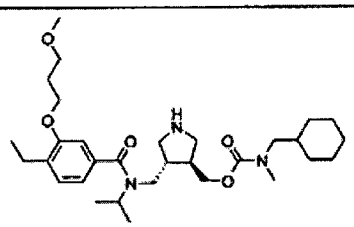
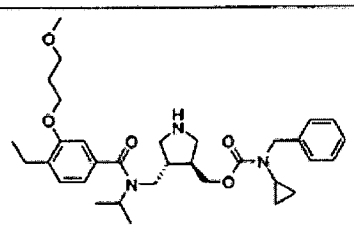
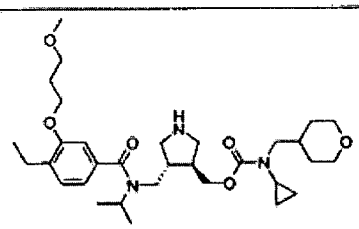
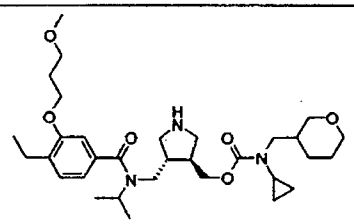
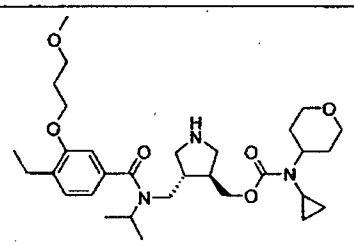
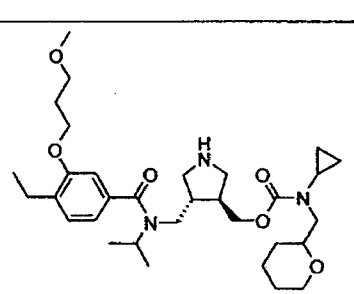
302	(3S, 4S)		562.3	1.07[b]

[a] t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto).

[b] t_R (HPLC Zorbax SB C18, del 10 al 95 por ciento de CH_3CN/H_2O/0.8 minutos, 95 por ciento de CH_3CN/0.7 minutos, CH_3CN y H_2O conteniendo HCOOH al 0.1 por ciento, flujo: 1.5 mililitros/minuto).

Los siguientes Ejemplos se preparan de acuerdo con los procedimientos descritos anteriormente para el Ejemplo 296, utilizando el terbutil-éster del ácido (3R,4S)-3-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-4-hidroxi-metil-pirrolidin-1-carboxílico:

Tabla 14

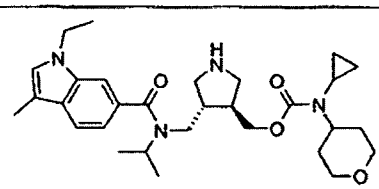
Ejemplo	Configuración	Estructura	$[M+H]^+$	t_R (HPLC)
303	(3S, 4S)		546.6	5.41[b]
304	(3S, 4S)		566.6	5.10[b]
305	(3S, 4S)		574.4	5.02[a]
306	(3S, 4S)		574.2	5.04[b] 5.13[b]
307	(3S, 4S)		560.3	4.94[a]
308	(3S, 4S)		574.2	4.87[b]

[a] t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto).

[b] t_R (Columna Nucleosil C18-HD, del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/1.5 minutos, flujo: 1 mililitro/minuto).

Los siguientes Ejemplos se preparan de acuerdo con los procedimientos descritos anteriormente para el Ejemplo 296, empezando a partir del terbutil-éster del ácido (3S,4R)-3-hidroxi-metil-4-({isopropil-[1-(3-metoxi-propil)-3-metil-1H-indol-6-carbonil]-amino}-metil)-pirrolidin-1-carboxílico:

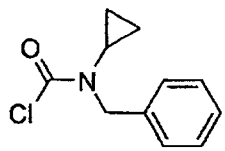
Tabla 15

Ejemplo	Configuración	Estructura	$[M+H]^+$	t_R (HPLC)
309	(3S, 4S)		569.3	2.39

t_R (HPLC, columna Waters Symmetry C18, del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/1.5 minutos).

Los intermediarios se preparan como se describe, mediante los siguientes métodos:

Cloruro de bencil-ciclopropil-carbamoílo



a. Bencil-ciclopropil-amina.

El compuesto del título se prepara de una manera análoga a la descrita para la bencil-ciclopropil-metil-amina. TLC, R_f (CH_2Cl_2/MeOH, 95:5) = 0.1. MS (LC-MS): 148.2 $[M+H]^+$.

b. Cloruro de bencil-ciclopropil-carbamoílo.

El compuesto del título se prepara de una manera análoga a la descrita para el cloruro de ciclohexil-metil-metil-carbamoílo. TLC, R_f (CH_2Cl_2/MeOH, 95:5) = 0.9. MS (LC-MS): 210.2. t_R (HPLC, columna Waters Symmetry C18, del 20 al 100 por ciento de CH_3CN/H_2O/5 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 0.6 mililitros/minuto): 4.67 minutos.

Cloruro de ciclopropil-(tetrahidro-piran-4-ilmetil)-carbamoílo

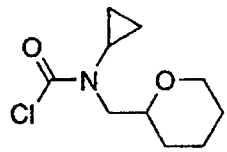
El compuesto del título se prepara de una manera análoga a la descrita para el cloruro de bencil-ciclopropil-carbamoílo, empezando a partir de ciclopropil-(tetrahidro-piran-4-ilmetil)-amina (preparada de una manera análoga a la descrita para la bencil-ciclopropil-metil-amina). TLC, R_f (CH_2Cl_2/MeOH, 95:5) = 0.9.

Cloruro de ciclopropil-(tetrahidro-piran-3-ilmetil)-carbamoílo

El compuesto del título se prepara de una manera análoga a la descrita para el cloruro de bencil-ciclopropil-carbamoílo,

empezando a partir de ciclopropil-(tetrahidro-piran-3-ilmetil)-amina (preparada de una manera análoga a la descrita para la bencil-ciclopropil-metil-amina). TLC, R_f (CH_2Cl_2/MeOH, 95:5) = 0.9.

Cloruro de ciclopropil-(tetrahidro-piran-2-ilmetil)-carbamoílo



a. Tetrahidro-piran-2-ilmetil-éster del ácido toluen-4-sulfónico.

A una suspensión de tetrahidropiran-2-metanol (2 gramos, 17.2 milimoles) enfriada a 0°C, se le agrega cloruro de toluen-4-sulfonilo (3.6 gramos, 18.92 milimoles), seguido por (2.63 mililitros, 18.92 milimoles) de trietil-amina. La mezcla se deja llegar a la temperatura ambiente, y se agita durante la noche. Luego se vierte en una solución acuosa saturada de $NaHCO_3$. Las capas se separan, y la acuosa se extrae dos veces con CH_2Cl_2. Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran, y se concentran. El material crudo se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente: ciclo-hexano/AcOEt, 80:20), para dar el producto del título. TLC, R_f (CH_2Cl_2/MeOH, 95:5) = 0.9. MS (LC-MS): 271.1 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, flujo: 1.5 mililitros/minuto): 5.32 minutos.

b. Ciclopropil-(tetrahidro-piran-2-ilmetil)-amina.

Una mezcla de tetrahidro-piran-2-ilmetil-éster del ácido toluen-4-sulfónico (500 miligramos, 185 milimoles) y ciclopropil-amina (2 mililitros, 15 milimoles), se calienta durante la noche a 110°C en un tubo sellado. La mezcla cruda se concentra y se recupera en CH_2Cl_2. Se agrega agua, se separan las capas, y la acuosa se retro-extrae dos veces con CH_2Cl_2. Los extractos orgánicos combinados se lavan con salmuera, se secan sobre Na_2SO_4, se filtran, y se concentran. TLC, R_f (CH_2Cl_2/MeOH, 95:5) = 0.3, MS (LC-MS): 156.2 $[M+H]^+$.

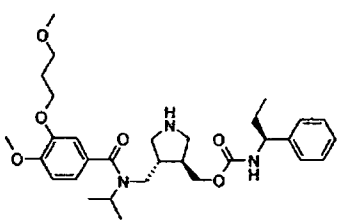
c. Cloruro de ciclopropil-(tetrahidro-piran-2-ilmetil)-carbamoílo.

A una solución agitada de ciclopropil-(tetrahidro-piran-2-ilmetil)-amina (200 miligramos, 0.74 milimoles) en tetrahidrofurano (4 mililitros), se le agregan trietil-amina (144 microlitros, 1.036 milimoles) y 4-dimetil-amino-piridina (1.81 miligramos, 0.015 milimoles). La mezcla se enfría a 0°C, y se agrega trifosgeno (88 miligramos, 0.296 milimoles) en una porción. Después de agitar durante 30 minutos a 0°C y durante la noche a temperatura ambiente, se agrega agua con precaución, y la solución se extrae con AcOEt. Los extractos orgánicos combinados se lavan con salmuera, se secan sobre Na_2SO_4, se filtran, y se concentran. TLC, R_f (CH_2Cl_2/MeOH, 95:5) = 0.9.

Cloruro de ciclopropil-(tetrahidro-piran-4-il)-carbamoílo

El compuesto del título se prepara de una manera análoga a la descrita para el cloruro de ciclopropil-(tetra-hidro-piran-2-ilmetil)-carbamoílo, empezando a partir de la ciclopropil-(tetrahidro-piran-4-il)-amina comercialmente disponible. TLC, R_f (CH_2Cl_2/MeOH, 95:5) = 0.9.

Ejemplo 310: (3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil-éster del ácido ((S)-1-fenil-propil)-carbámico



A una solución de terbutil-éster del ácido (3R,4S)-3-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil-4-((S)-1-fenil-propil-carbamoiloxi-metil)-pirrolidin-1-carboxílico (49 miligramos, 0.075 milimoles) en 1 mililitro de dioxano, se le agrega HCl 4N en dioxano (0.5 mililitros, 2 milimoles). La mezcla se agita a temperatura ambiente durante 2 horas, y la solución resultante se liofiliza para proporcionar la sal de clorhidrato correspondiente. MS (LC-MS): 556.3 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18-HD, del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/1.5 minutos, flujo: 1 mililitro/minuto): 4.11 minutos.

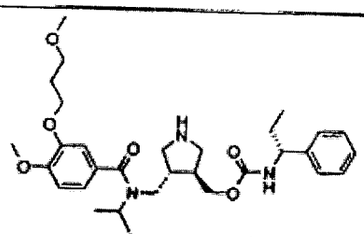
El material de inicio se prepara como sigue:

Terbutil-éster del ácido (3R,4S)-3-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-4-((S)-1-fenil-propil-carbamoiloxi-metil)-pirrolidin-1-carboxílico.

A una solución del terbutil-éster del ácido (3S,4R)-3-hidroxi-metil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (200 mili-gramos, 0.404 milimoles) en éter (12 mililitros), se le agregan sucesivamente isocianato de (S)-1-fenil-propilo (130.4 miligramos, 0.809 milimoles) y $AlCl_3$ (54 miligramos, 0.404 milimoles). La mezcla se agita a temperatura ambiente bajo nitrógeno durante la noche. Se agregan nuevamente isocianato de (S)-1-fenil-propilo (150 microlitros) y $AlCl_3$ (54 miligramos, 0.404 milimoles), y la mezcla se agita adicionalmente durante 5 horas. Se agrega AcOEt, y la mezcla de reacción se apaga mediante la adición de una solución acuosa saturada de $NaHCO_3$. Las capas se separan, y la acuosa se retro-extrae dos veces con AcOEt. Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran, y se concentran bajo presión reducida. La mezcla cruda se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente: CH_2Cl_2/MeOH, de 100:0 a 95:5), para dar el producto del título. TLC, R_f (CH_2Cl_2/MeOH, 95:5) = 0.35. MS (LC-MS): 656.2 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18-HD, del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/1.5 minutos, flujo: 1 mililitro/minuto): 3.94 minutos.

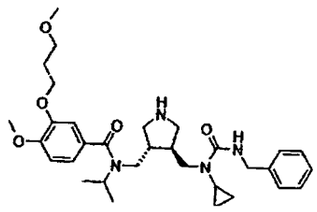
Los siguientes Ejemplos se preparan de acuerdo con los procedimientos descritos anteriormente para el Ejemplo 310:

Tabla 16

Ejemplo	Configuración	Estructura	$[M+H]^+$	t_R (HPLC)
311	(3S, 4S)		556.3	4.13

t_R (HPLC, columna Nucleosil C18-HD, del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/1.5 minutos, flujo: 1 mililitro/minuto).

Ejemplo 312: N-[(3S*,4S*)-4-(3-bencil-1-ciclopropil-ureido-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida



A una solución de terbutil-éster del ácido (3R*,4R*)-3-(3-bencil-1-ciclopropil-ureido-metil)-4-({iso-propil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (270 miligramos, 0.405 milimoles) en dioxano (5 mililitros), se le agrega HCl 4N en dioxano (3 mili-litros), y la solución resultante se agita

a temperatura ambiente durante 5 horas. La liofilización proporciona la sal de clorhidrato correspondiente como un polvo incoloro. MS (LC-MS): 567.0 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.18 minutos.

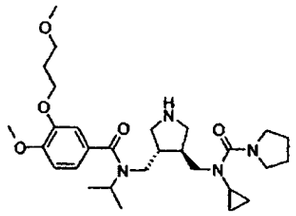
El material de inicio se prepara como sigue:

Terbutil-éster del ácido (3R*,4R*)-3-(3-bencil-1-ciclo-propil-ureido-metil)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico.

A una solución del terbutil-éster del ácido ((3R*,4R*)-3-ciclopropil-amino-metil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (235 miligramos, 0.440 milimoles) en tetrahidro-furano (6 mililitros), se le agrega trietil-amina (123 micro-litros, 0.880 milimoles), seguida por isocianato de bencilo (54 microlitros, 0.440 milimoles). La mezcla se agita a temperatura ambiente durante 2 horas antes de agregar agua. La extracción con acetato de etilo, el secado de los extractos combinados (Na_2SO_4), la filtración, y la evaporación del solvente, proporciona el producto crudo, el cual se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente, gradiente: 100 por ciento de CH_2Cl_2 hasta CH_2Cl_2/MeOH, 9:1), para dar el compuesto del título. MS (LC-MS): 667.1 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-

Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1 mililitro/minuto): 6.26 minutos.

Ejemplo 313: Ciclopropil-[(3S*,4S*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido pirrolidin-1-carboxílico



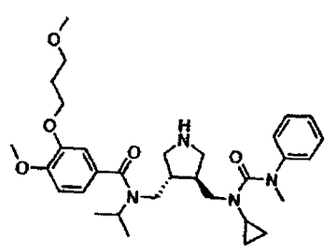
A una solución del terbutil-éster del ácido (3R*,4R*)-3-{[ciclopropil-(pirrolidin-1-carbonil)-amino]-metil}-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (165 miligramos, 0.262 mili-moles) en dioxano (5 mililitros), se le agrega HCl 4N en dioxano (3 mililitros), y la solución resultante se agita a temperatura ambiente durante 4.5 horas. La liofilización proporciona la sal de clorhidrato correspondiente como un sólido incoloro. MS (LC-MS): 531.1 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.11 minutos.

El material de inicio se prepara como sigue:

Terbutil-éster del ácido (3R*,4R*)-3-{[ciclopropil-(pirrolidin-1-carbonil)-amino]-metil}-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico.

Se agrega trietil-amina (99 microlitros, 0.714 mili-moles), seguida por cloruro de 1-pirrolidin-carbonilo, a una solución de terbutil-éster del ácido ((3R*,4R*)-3-ciclopropil-amino-metil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (254 mili-gramos, 0.476 milimoles) en CH_2Cl_2 (20 mililitros). La solución resultante se agita a temperatura ambiente durante 2 horas, y a 60°C durante otras 24 horas. La evaporación del solvente proporciona el producto crudo, el cual se purifica mediante HPLC de preparación (Waters C_{18} ODB, eluyente: H_2O/CH_3CN, del 20 al 100 por ciento), para dar el compuesto del título. MS (LC-MS): 631.1 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 6.31 minutos.

Ejemplo 314: N-[(3S*,4S*)-4-(1-ciclopropil-3-metil-3-fenil-ureido-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida



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Una solución de terbutil-éster del ácido (3R*,4R*)-3-(1-ciclopropil-3-metil-3-fenil-ureido-metil)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (195 miligramos, 0.29 milimoles) en HCl 4N/ dioxano (8 mililitros), se agita a temperatura ambiente, hasta que se termina la reacción. La liofilización proporciona el compuesto del título como una espuma incolora. MS (LC-MS): 567.1 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1.5 mililitros/ minuto): 4.57 minutos.

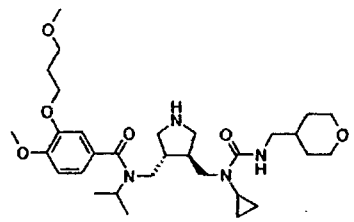
El material de inicio se prepara como sigue:

Terbutil-éster del ácido (3R*,4R*)-3-(1-ciclopropil-3-metil-3-fenil-ureido-metil)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico.

Una mezcla del terbutil-éster del ácido (3R*,4R*)-3-ciclopropil-amino-metil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (216 miligramos, 0.41 milimoles), cloruro de N-metil-N-fenil-carbamoílo (274 miligramos, 1.62 milimoles), trietil-amina (0.45 mililitros, 3.24 milimoles), y DMAP (1 miligramo, 0.008 milimoles) en tetrahidrofurano (15 mililitros), se calienta a 60°C durante 4 horas. Después de enfriarse a temperatura ambiente, se agrega HCl 1N, y la mezcla se extrae con acetato de etilo, los extractos orgánicos combinados se secan (Na_2SO_4), se filtran, y se evapora el

solvente. La purificación mediante cromatografía por evaporación instantánea (eluyente, gradiente: 100 por ciento de CH_2Cl_2 hasta CH_2Cl_2/MeOH, 9:1) proporciona el compuesto del título. MS (LC-MS): 667.1 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 6.02 minutos.

Ejemplo 315: N-{(3S,4S)-4-[1-ciclopropil-3-(tetrahidro-piran-4-ilmetil)-ureido-metil]-pirrolidin-3-ilmetil}-N-iso-propil-4-metoxi-3-(3-metoxi-propoxi)-benzamida



A una solución del terbutil-éster del ácido (3R*,4R*)-3-[1-ciclopropil-3-(tetrahidro-piran-4-ilmetil)-ureido-metil]-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (50 miligramos, 0.074 milimoles) en dioxano (3 mililitros), se le agrega HCl 4N en dioxano (1 mililitro), y la solución resultante se agita a temperatura ambiente durante 5 horas. La liofilización proporciona la sal de clorhidrato correspondiente como un sólido incoloro. MS (LC-MS): 575.1 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético

al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.29 minutos.

El material de inicio se prepara como sigue:

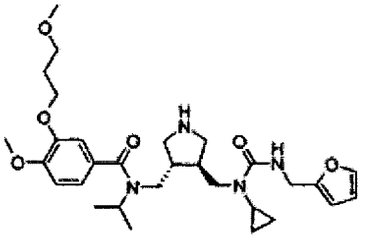
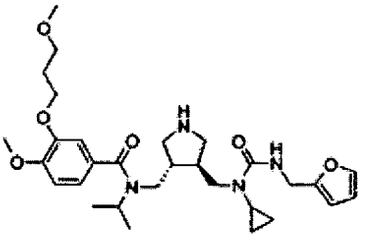
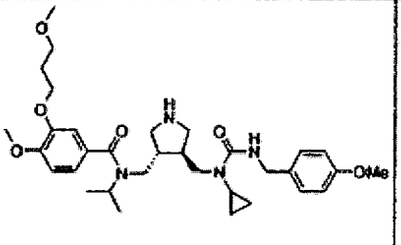
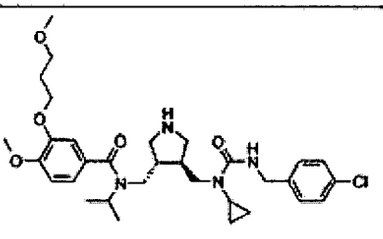
Terbutil-éster del ácido (3R*,4R*)-3-[1-ciclopropil-3-(tetra-hidro-piran-4-ilmetil)-ureido-metil]-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico.

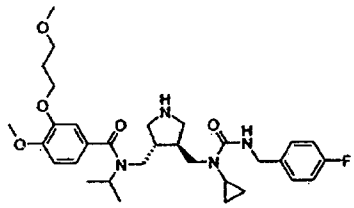
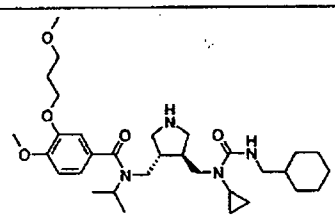
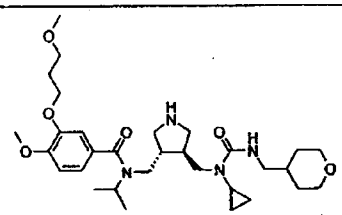
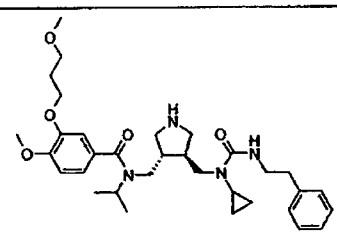
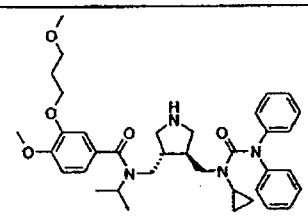
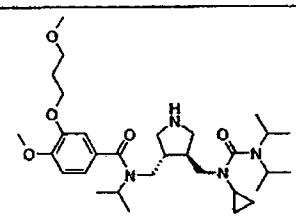
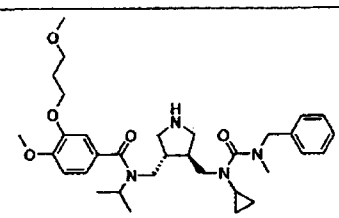
Se agrega 4-amino-metil-tetrahidropirano (50 mili-gramos, 0.435 milimoles) a una suspensión de carbonato de bis-(tricloro-metilo) (155 miligramos, 0.522 milimoles) y carbón (10 miligramos) en AcOEt (8 mililitros) a temperatura ambiente. La mezcla se agita a temperatura ambiente durante 5 minutos, y se calienta bajo reflujo durante otros 10 minutos antes de dejarse enfriar a temperatura ambiente. La filtración y la evaporación del solvente proporcionan el isocianato correspondiente, el cual se utiliza sin mayor purificación, y se disuelve en CH_3CN (10 mililitros). Se agrega el terbutil-éster del ácido ((3R*,4R*)-3-ciclopropil-amino-metil-4-({iso-propil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (232 miligramos, 0.435 milimoles), y la mezcla se calienta bajo reflujo durante 16 horas. Para el procesamiento, el solvente se evapora y se purifica mediante HPLC de preparación (Interchrom C_{18} ODB, eluyente: 5 por ciento de CH_3CN/H_2O/2.5 minutos, del 5 al 100 por ciento de CH_3CN/H_2O/22.5 minutos, 100 por ciento de CH_3CN/4.5 minutos, flujo: 40 mililitros/minuto), para dar el compuesto del título. MS (LC-MS): 675.1 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5

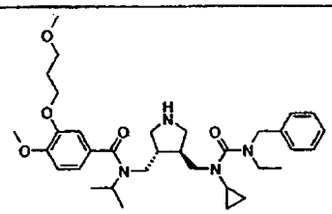
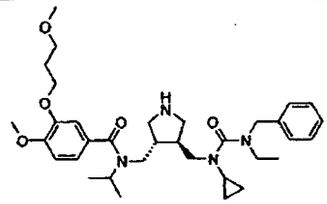
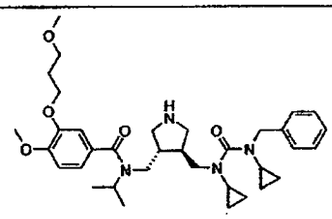
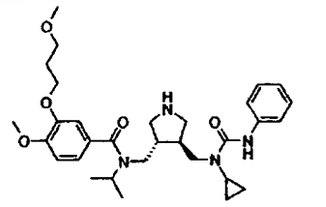
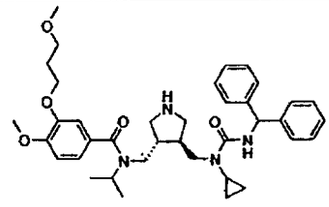
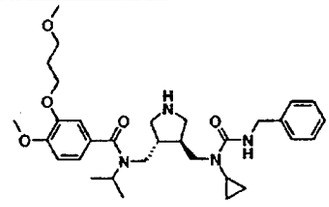
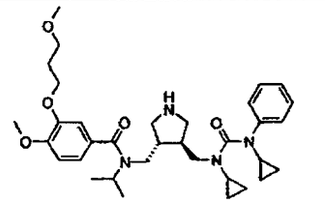
minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 6.19 minutos.

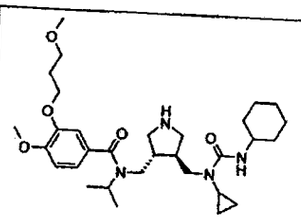
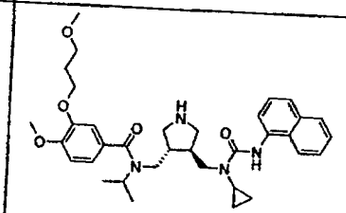
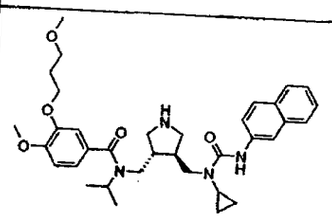
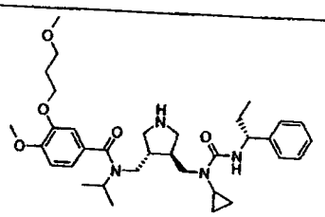
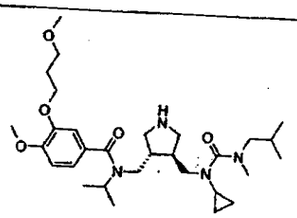
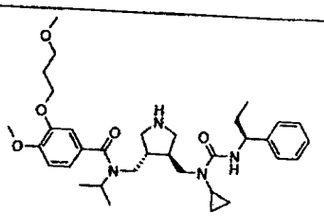
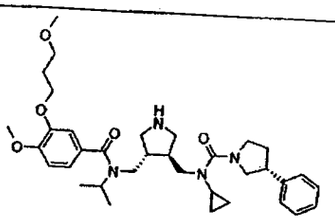
Los siguientes Ejemplos se preparan de acuerdo con los procedimientos descritos anteriormente para el Ejemplo 312 o para el Ejemplo 314:

Tabla 17

Ejemplo	Configuración	Estructura	$[M+H]^+$	t_R (HPLC)
316	(3S*, 4S*)		557.0	5.17[a]
317	(3S, 4S)		557.5	4.77[a]
318	(3S*, 4S*)		597.1	5.35[a]
319	(3S*, 4S*)		601.0	5.58[a]

320	(3S*, 4S*)		585.0	5.42[a]
321	(3S*, 4S*)		573.1	5.73[a]
322	(3S*, 4S*)		575.1	5.29[a]
323	(3S*, 4S*)		581.1	5.67[a]
324	(3S*, 4S*)		629.1	5.85[a]
325	(3S*, 4S*)		561.1	5.70[a]
326	(3S*, 4S*)		581.1	4.66[a]

327	(3S*, 4S*)		595.1	4.78[a]
328	(3S, 4S)		595.0	5.04[a]
329	(3S*, 4S*)		607.5	4.96[a]
330	(3S*, 4S*)		553.3	4.74[a]
331	(3S*, 4S*)		643.2	5.17[a]
332	(3S, 4S)		567.3	4.82[a]
333	(3S*, 4S*)		593.3	4.94[a]

334	(3S*, 4S*)		559.5	5.05[a]
335	(3S*, 4S*)		603.3	5.52[a]
336	(3S, 4S)		603.3	5.95[a]
337	(3S, 4S)		595.2	5.85[a]
338	(3S, 4S)		547.2	5.91[a]
339	(3S, 4S)		595.2	5.13[a]
340	(3S, 4S)		607.5	3.47[b]

[a] t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 0.6 mililitros/ minuto).

[b] t_R (HPLC, Columna Waters Symmetry C18, del 10 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/H_2O, 2 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 0.6 mililitros/ minuto).

Cloruro de bencil-metil-carbamoílo

A -78°C, se agrega piridina (1.25 mililitros, 15.5 milimoles), seguida por metil-bencil-amina (2.0 mililitros, 15.5 milimoles), a una solución de carbonato de bis-(tricloro-metilo) (1.55 gramos, 5.2 milimoles) en CH_2Cl_2 (20 mililitros). La mezcla de reacción se deja calentar a temperatura ambiente, y se agita durante otras 1.5 horas. Para el procesamiento, se agrega HCl 1N a la suspensión amarilla, y la mezcla se extrae con acetato de etilo. El secado (Na_2SO_4) de los extractos orgánicos combinados, la filtración, y la evaporación del solvente, proporcionan el compuesto del título. MS (LC-MS): $[M+H]^+$ = 184.1. t_R (HPLC, columna Waters Symmetry C18, del 20 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/H_2O, 2 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 0.6 mililitros/minuto): 3.84 minutos.

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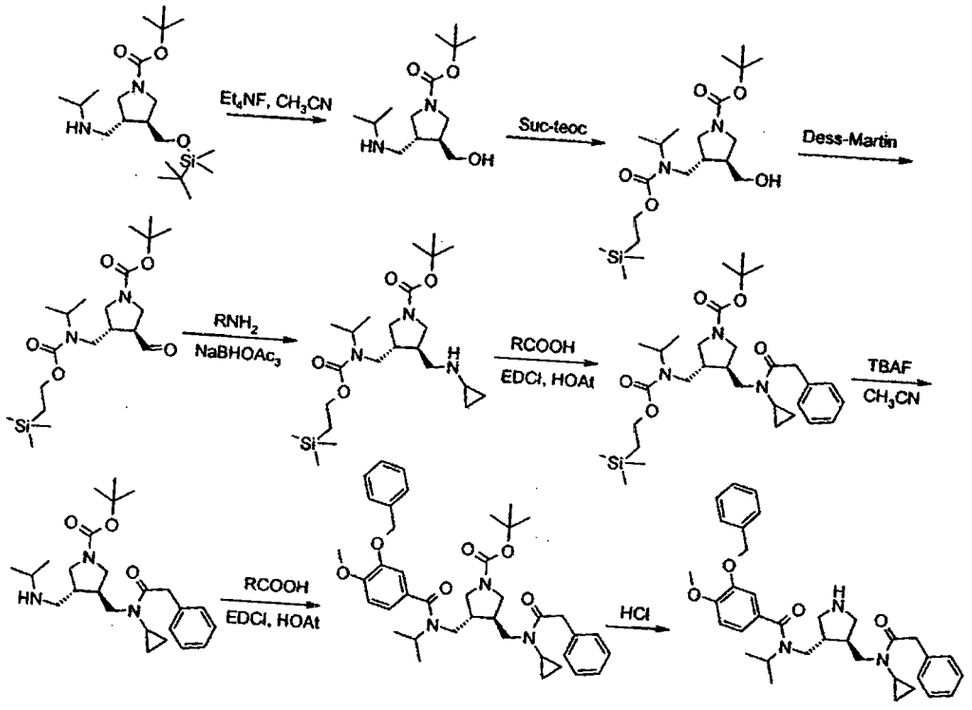
Cloruro de bencil-etil-carbamoílo

El compuesto del título se prepara de una manera análoga a la descrita para el cloruro de bencil-metil-carbamoílo a partir de bencil-etil-amina. MS (LC-MS): $[M+H]^+$ = 198.1. t_R (HPLC, columna Waters Symmetry C18, del 20 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/H_2O, 2 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 0.6 mililitros/ minuto): 4.12 minutos.

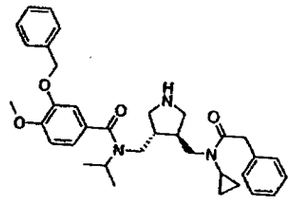
Cloruro de fenil-ciclopropil-carbamoílo

El compuesto del título se prepara de una manera análoga a la descrita para el cloruro de bencil-metil-carbamoílo, a partir de ciclopropil-fenil-amina, preparada de acuerdo con Synlett 2003, 14, 2139. MS (LC-MS): $[M+H]^+$ = 196.2. t_R (HPLC, columna Waters Symmetry C18, del 20 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/H_2O), 2 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 0.6 mililitros/ minuto): 4.44 minutos.

Esquema de reacción 6



Ejemplo 341: 3-benciloxi-N-{(3S,4S)-4-[(ciclopropil-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-N-isopropil-4-metoxi-benzamida



A una solución de terbutil-éster del ácido (3R,4R)-3-{[(3-benciloxi-4-metoxi-benzoil)-isopropil-amino]-metil}-4-[(ciclopropil-fenil-acetil-amino)-metil]-pirrolidin-1-carboxílico (0.191 gramos, 0.285 milimoles) en dioxano (2 mililitros), se le agrega HCl 4N en dioxano (1.07 mililitros), y la solución resultante se agita durante 2

horas, y luego se liofiliza para proporcionar la sal de clorhidrato correspondiente. MS (LC-MS): 570.2 $[M+H]^+$; t_R (HPLC, columna C18, del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/1.5 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1 mililitro/minuto): 4.60 minutos.

El material de inicio se prepara como sigue:

A. Terbutil-éster del ácido (3S,4R)-3-hidroxi-metil-4-(iso-propil-amino-metil)-pirrolidin-1-carboxílico.

A una solución del terbutil-éster del ácido (3S,4R)-3-(terbutil-dimetil-silaniloxi-metil)-4-(isopropil-amino-metil)-pirrolidin-1-carboxílico (preparado de acuerdo con F del Ejemplo 9, Esquema de reacción 5) (19.5 gramos, 47.4 milimoles) en MeCN (250 mililitros), se le agrega Et_4NF (14.4 gramos, 94.8 milimoles), y el producto resultante se pone a reflujo durante 3 horas. El solvente se concentra bajo presión reducida, y el material crudo se recupera en AcOEt; se agrega una solución acuosa saturada de $NaHCO_3$, y se separan las capas. La capa acuosa se retro-extrae dos veces con AcOEt, y los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran, y se concentran. El compuesto se utiliza en el siguiente paso sin mayor purificación. TLC, R_f ($MeOH/CH_2Cl_2$, 1:9): 0.22. MS (LC-MS): 273.0 $[M+H]^+$.

B. Terbutil-éster del ácido (3S,4S)-3-hidroxi-metil-4-{[iso-propil-(2-trimetil-silanil-etoxi-carbonil)-amino]-metil}-pirrolidin-1-carboxílico.

A una solución del terbutil-éster del ácido (3S,4R)-3-hidroxi-metil-4-(isopropil-amino-metil)-pirrolidin-1-carboxílico (13.6 gramos, 47.4 milimoles) en dioxano (200 mililitros), se le agregan Et_3N (6.64 mililitros, 47.4 milimoles) y 1-[(2-trimetil-silil)-etoxi-carboniloxi]-pirrolidin-2,5-diona (12.3 gramos, 47.4 milimoles). La mezcla se agita durante la noche a temperatura ambiente bajo nitrógeno. El solvente se concentra bajo presión reducida, y el material crudo se recupera en AcOEt, se agrega una solución acuosa saturada de $NaHCO_3$, y se separan las capas. La capa acuosa se retro-extrae dos veces con AcOEt, y los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran, y se concentran. El residuo crudo se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente: CH_2Cl_2/MeOH, 95:5), para proporcionar el compuesto del título como un aceite amarillo. TLC, R_f (MeOH/CH_2Cl_2, 2:8): 0.65. MS (LC-MS): 417.0 $[M+H]^+$.

C. Terbutil-éster del ácido (3S,4S)-3-formil-4-{[isopropil-(2-trimetil-silanil-etoxi-carbonil)-amino]-metil}-pirrolidin-1-carboxílico.

A una mezcla bien agitada de terbutil-éster del ácido (3S,4S)-3-hidroxi-metil-4-{[isopropil-(2-trimetil-silanil-etoxi-carbonil)-amino]-metil}-pirrolidin-1-carboxílico (16.6 gramos, 39.8 milimoles) y peryodinano de Dess-Martin (16.9 gramos, 39.8 milimoles) en CH_2Cl_2 (110 mililitros), se le agrega CH_2Cl_2 lentamente humedecido (0.79 mililitros de agua en 110 mililitros de

CH_2Cl_2). La solución transparente se hace nebulosa hacia el final de la adición de CH_2Cl_2 húmedo, y se agita adicionalmente durante la noche. Luego se concentra hasta unos cuantos mililitros de solvente mediante evaporación giratoria, y se recupera en Et_2O. Se agrega una solución de 1:1 de $Na_2S_2O_3$ al 10 por ciento/$NaHCO_3$ acuoso saturado. Las capas se separan, y el extracto orgánico se lava sucesivamente con H_2O y salmuera. Los lavados acuosos se retro-extraen con Et_2O, y esta capa orgánica se lava con H_2O y salmuera. Las capas orgánicas combinadas se secan con Na_2SO_4, se filtran, y se concentran. La mezcla cruda se utiliza en el siguiente paso sin mayor purificación. TLC, R_f (CH_2Cl_2/MeOH, 9:1) = 0.48. MS (LC-MS): 437.0 $[M+Na]^+$.

D. Terbutil-éster del ácido (3R,4S)-3-ciclopropil-amino-metil-4-{[isopropil-(2-trimetil-silanil-etoxi-carbonil)-amino]-metil}-pirrolidin-1-carboxílico.

A una solución del terbutil-éster del ácido (3S,4S)-3-formil-4-{[isopropil-(2-trimetil-silanil-etoxi-carbonil)-amino]-metil}-pirrolidin-1-carboxílico (8.1 gramos, 19.5 mili-moles) y ciclopropil-amina (1.54 mililitros, 21.5 milimoles) en 1,2-dicloro-etano (200 mililitros), se le agrega $NaBH(OAc)_3$ (6.1 gramos, 27.3 milimoles), y la mezcla se agita durante la noche. Entonces se diluye con CH_2Cl_2, y se lava con una solución acuosa saturada de $NaHCO_3$. La capa acuosa se retro-extrae dos veces con CH_2Cl_2, y los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran, y se concentran. El material crudo se utiliza en el siguiente paso

sin mayor purificación. TLC, R_f (CH_2Cl_2/MeOH, 9:1) = 0.45. MS (LC-MS): 456.2 $[M+H]^+$.

E. Terbutil-éster del ácido (3R,4S)-3-[(ciclopropil-fenil-acetil-amino)-metil]-4-{[isopropil-(2-trimetil-silanil-etoxi-carbonil)-amino]-metil}-pirrolidin-1-carboxílico.

A una solución de ácido fenil-acético (1.45 gramos, 10.53 milimoles) y terbutil-éster del ácido (3R,4S)-3-ciclo-propil-amino-metil-4-{[isopropil-(2-trimetil-silanil-etoxi-carbonil)-amino]-metil}-pirrolidin-1-carboxílico (3.2 gramos, 7.022 milimoles) en CH_2Cl_2 (10 mililitros), se le agregan trietil-amina (1.47 mililitros, 10.53 milimoles) e hidrato de 1-hidroxi-7-aza-benzotriazol (1.46 gramos, 10.53 milimoles), seguidos 15 minutos después por clorhidrato de N-(3-dimetil-amino-propil)-N'-etil-carbodi-imida (3.06 gramos, 15.78 mili-moles). La mezcla resultante se agita durante 2 días a temperatura ambiente, luego se diluye con CH_2Cl_2, y se vierte en una solución acuosa de HCl 2M. Las capas se separan, y la capa acuosa se extrae dos veces con CH_2Cl_2. Los extractos orgánicos combinados se neutralizan con una solución acuosa saturada de $NaHCO_3$, se secan sobre Na_2SO_4, se filtran, y se concentran. El producto crudo se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente: hexano/AcOEt, 2:1). TLC, R_f (hexano/AcOEt, 1:1) = 0.42. MS (LC-MS): 574.2 $[M+H]^+$; t_R (HPLC, columna C18, del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/1.5 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1

mililitro/minuto): 6.49 minutos.

F. Terbutil-éster del ácido (3R,4R)-3-[(ciclopropil-fenil-acetil-amino)-metil]-4-(isopropil-amino-metil)-pirrolidin-1-carboxílico.

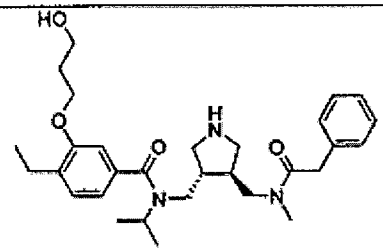
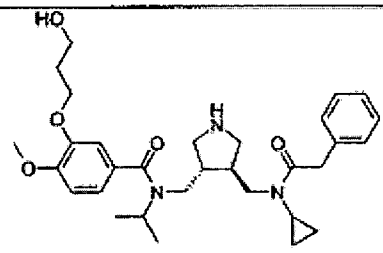
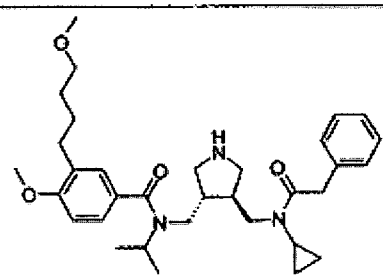
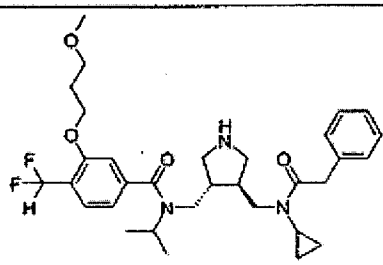
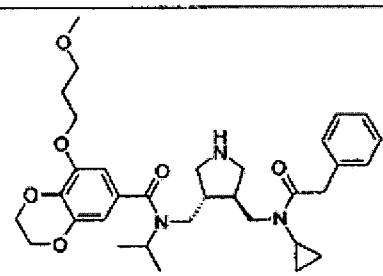
A una solución del terbutil-éster del ácido (3R,4S)-3-[(ciclopropil-fenil-acetil-amino)-metil]-4-{[isopropil-(2-trimetil-silanil-etoxi-carbonil)-amino]-metil}-pirrolidin-1-carboxílico (2.55 gramos, 4.44 milimoles) en CH_3CN (30 mili-litros), se le agrega trihidrato de fluoruro de tetrabutil-amonio (4.34 gramos, 13.33 milimoles) bajo una atmósfera de nitrógeno. La mezcla de reacción se agita durante la noche a reflujo. El solvente se retira al vacío, y se agregan agua y CH_2Cl_2, las capas se separan, y la acuosa se extrae dos veces con CH_2Cl_2. Los extractos orgánicos combinados se secan (Na_2SO_4), y el solvente se retira al vacío. El producto crudo se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente: CH_2Cl_2/MeOH/NH_4OH, 98:2:1), para dar el producto del título. TLC, R_f (CH_2Cl_2/MeOH/NH_4OH, 98:2:1) = 0.11. MS (LC-MS): 430.2 $[M+H]^+$; t_R (HPLC, columna C18, del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/1.5 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1 mililitro/minuto): 3.90 minutos.

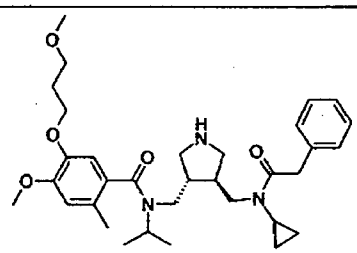
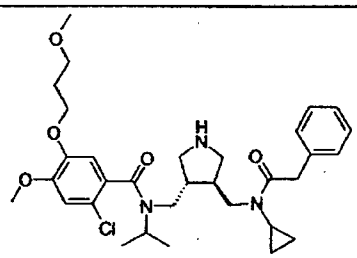
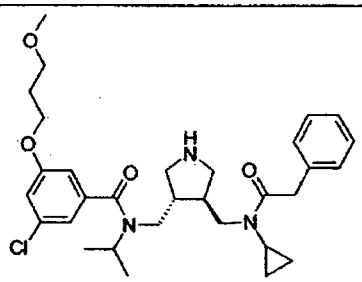
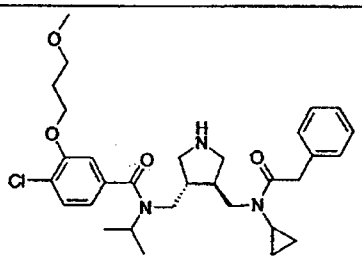
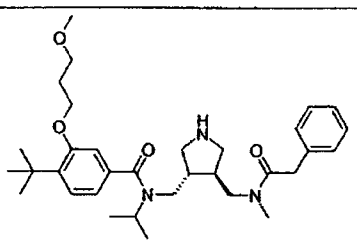
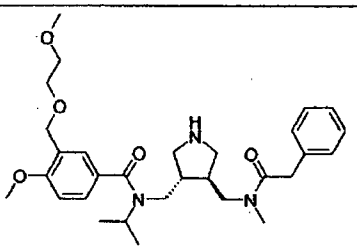
G. Terbutil-éster del ácido (3R,4R)-3-{[(3-benciloxi-4-metoxi-benzoil)-isopropil-amino]-metil}-4-[(ciclopropil-fenil-acetil-amino)-metil]-pirrolidin-1-carboxílico.

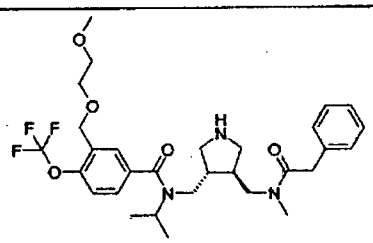
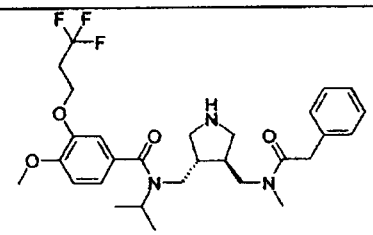
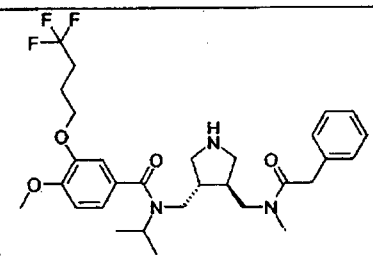
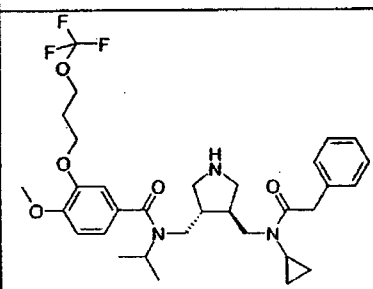
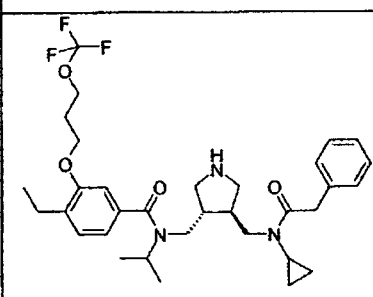
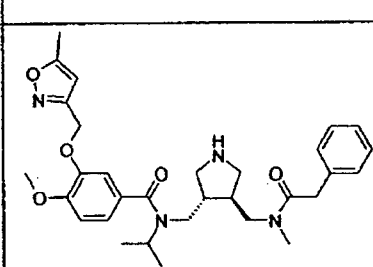
A una solución de ácido 3-benciloxi-4-metoxi-benzoico (0.19 gramos, 0.734 milimoles) y terbutil-éster del ácido (3R,4R)-3-[(ciclopropil-fenil-acetil-amino)-metil]-4-(iso-propil-amino-metil)-pirrolidin-1-carboxílico (0.3 gramos, 0.489 milimoles) en CH_2Cl_2 (10 mililitros), se le agregan trietil-amina (0.102 mililitros, 0.734 milimoles) e hidrato de 1-hidroxi-7-aza-benzotriazol (0.102 gramos, 0.734 milimoles), seguidos 15 minutos después por clorhidrato de N-(3-dimetil-amino-propil)-N'-etil-carbodi-imida (0.142 gramos, 0.734 mili-moles). La mezcla resultante se agita durante 2 días a temperatura ambiente, luego se diluye con CH_2Cl_2, y se vierte en una solución acuosa de HCl 2M. Las capas se separan, y la acuosa se extrae dos veces con CH_2Cl_2. Los extractos orgánicos combinados se neutralizan con una solución acuosa saturada de $NaHCO_3$, se secan sobre Na_2SO_4, se filtran, y se concentran. El producto crudo se purifica mediante HPLC de preparación. MS (LC-MS): 670.2 $[M+H]^+$; t_R (HPLC, columna C18, del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/1.5 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1 mililitro/ minuto): 5.76 minutos.

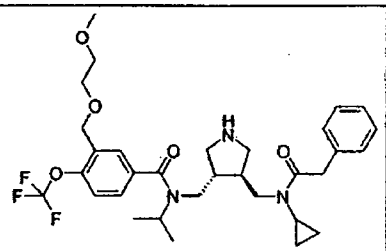
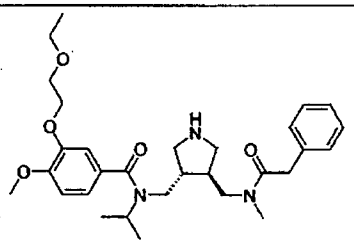
Los siguientes Ejemplos se preparan de acuerdo con los procedimientos descritos anteriormente para el Ejemplo 341, empezando a partir de terbutil-éster del ácido (3R,4R)-3-[(bencil-ciclopropil-amino)-metil]-4-(isopropil-amino-metil)-pirrolidin-1-carboxílico (o su racemato), y el ácido benzoico sustituido correspondiente.

Tabla 18:

Ejemplo	Configuración	Estructura	$[M+H]^+$	t_R (HPLC)
342	(3S, 4S)		510.4	4.63[a]
343	(3S,4S)		538.2	3.47[c]
344	(3S*, 4S*)		550.2	4.66[c]
345	(3S*, 4S*)		572.2	4.71[c]
346	(3S*, 4S*)		580.2	4.14[c]

347	(3S*, 4S*)		566.2	4.23[c]
348	(3S*, 4S*)		586.2	4.46[c]
349	(3S*, 4S*)		556.2	4.79[c]
350	(3S*, 4S*)		556.2	4.86[c]
351	(3S,4S)		552.4	5.56[b]
352	(3S,4S)		526.2	3.66[c]

353	(3S,4S)		580.2	4.88[b]
354	(3S,4S)		550.2	4.06[c]
355	(3S,4S)		564.2	4.30[c]
356	(3S,4S)		606.2	4.63[c]
357	(3S,4S)		604.2	5.30[b]
358	(3S,4S)		549.2	4.48[b]

359	(3S,4S)		606.2	5.07[a]
360	(3S,4S)		526.2	4.40[a]

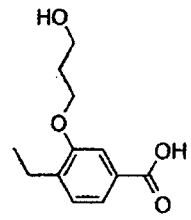
[a] t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1.5 mililitros/minuto).

[b] t_R (Columna Nucleosil C18HD, del 5 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto).

[c] t_R (Columna Nucleosil C18HD, del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto).

Se preparan los siguientes intermediarios:

Ácido 4-etil-3-(3-hidroxi-propoxi)-benzoico



a. Ácido 4-etil-3-hidroxi-benzoico.

A una solución de ácido 4-etil-3-(3-metoxi-propoxi)-benzoico (6.44 gramos, 27.03 milimoles) en CH_2Cl_2 (150 mili-litros) a -78°C, se le agrega lentamente BBr_3 (9 mililitros, 93.41 milimoles). La mezcla de reacción se deja llegar a la temperatura ambiente, y se agita durante 3 horas; luego se vierte en agua helada y se filtra para proporcionar el producto del título como un sólido blanco. TLC, R_f (CH_2Cl_2/ MeOH, 95:5) = 0.2.

b. Metil-éster del ácido 4-etil-3-hidroxi-benzoico.

A una solución del ácido 4-etil-3-hidroxi-benzoico (3.76 gramos, 22.6 milimoles) en MeOH (70 mililitros), se le agrega H_2SO_4 concentrado (0.7 mililitros). La solución se pone a reflujo durante la noche, luego se concentra hasta aproximadamente 30 mililitros, y se vierte en agua. La capa acuosa se extrae con éter (50 mililitros, cuatro veces), y los extractos orgánicos combinados se neutralizan con una solución acuosa saturada de $NaHCO_3$ (50 mililitros, dos veces), se lava con salmuera (50 mililitros), se seca sobre Na_2SO_4, se filtra, y se concentra, para dar el compuesto del título como un polvo blanco. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.7,

MS (LC-MS): 179.2 $[M+H]^-$, t_R (HPLC, columna Nucleosil C18, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/2.8 minutos, flujo: 1 mililitro/minuto): 4.86 minutos.

c. Metil-éster del ácido 4-etil-3-(3-hidroxi-propoxi)-benzoico.

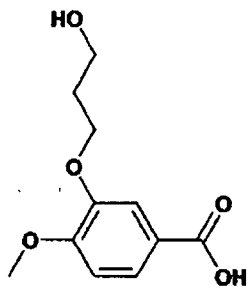
A una solución del metil-éster del ácido 4-etil-3-hidroxi-benzoico (3.21 gramos, 17.81 milimoles) en acetonitrilo (35 mililitros), se le agregan 3-bromo-1-propanol (1.85 mililitros, 21.37 milimoles) y K_2CO_3 (3.69 gramos, 26.7 milimoles). La solución se pone a reflujo durante 4 horas, luego se vierte en agua, y se extrae tres veces con AcOEt. Los extractos orgánicos combinados se lavan con salmuera, se secan sobre Na_2SO_4, se filtran, y se concentran, para dar el producto del título. TLC, R_f (c-hexano/AcOEt 8:2) = 0.15, MS (LC-MS): 239.2 $[M+H]^+$, t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, flujo: 1.5 mililitros/minuto): 5.10 minutos.

d. Ácido 4-etil-3-(3-hidroxi-propoxi)-benzoico.

Una solución del metil-éster del ácido 4-etil-3-(3-hidroxi-propoxi)-benzoico (4.68 gramos, 19.63 milimoles) en MeOH (90 mililitros) y H_2O (5 mililitros), se trata con NaOH (2.35 gramos, 58.89 milimoles), y se calienta a reflujo durante 5 horas. La mezcla de reacción se extrae con AcOEt, y la capa acuosa se acidifica con HCl 4N, y se extrae tres veces con CH_2Cl_2. Los

extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran, y se concentran al vacío, para dar el producto del título. TLC, R_f (CH_2Cl_2/MeOH 95:5) = 0.1, MS (LC-MS): 223.1 $[M-H]^-$, t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, flujo: 1.5 mililitros/minuto): 4.47 minutos.

Ácido 3-(3-hidroxi-propoxi)-4-metoxi-benzoico



a. Metil-éster del ácido 3-(3-hidroxi-propoxi)-4-metoxi-benzoico.

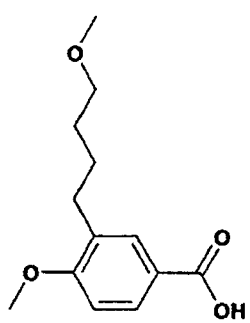
Una mezcla de 3-hidroxi-4-metoxi-benzoato de metilo (4.94 gramos, 26.6 milimoles), 3-bromo-1-propanol (2.86 mililitros, 31.9 milimoles), y K_2CO_3 anhidro (5.51 gramos, 39.9 milimoles) en MeCN (50 mililitros) se pone a reflujo con agitación durante la noche, y después de enfriarse, se vierte en hielo/agua. La capa acuosa se extrae con AcOEt, y los orgánicos combinados se lavan con salmuera, se secan (Na_2SO_4), y se concentran. La purificación mediante cromatografía por evaporación instantánea sobre gel de sílice (hexano/AcOEt 1:2), da un residuo sólido, el cual se agita en una mezcla de 9:1 de hexano/AcOEt durante 30 minutos. La filtración de la suspensión y el secado al vacío dan el compuesto

del título como un sólido blanco. TLC, R_f (hexano/AcOEt 1:1) = 0.09. MS: 241.2 $[M+H]^+$, t_R (HPLC, columna Nucleosil C18HD, del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1 mililitro/minuto): 2.86 minutos. ^1H RMN ($CDCl_3$): δ 2.13 (m, 2H), 2.59 (m, 1H), 3.92 (s, 3H), 3.93 (s, 3H), 4.29 (m, 2H), 6.92 (m, 1H), 7.60 (s, 1H), 7.73 (m, 1H) ppm.

b. Ácido 3-(3-hidroxi-propoxi)-4-metoxi-benzoico.

Una solución del metil-éster del ácido 3-(3-hidroxi-propoxi)-4-metoxi-benzoico (1.00 gramos, 4.16 milimoles) en tetrahidrofurano (3.0 mililitros) y NaOH 2N (3.1 mililitros) se agita a temperatura ambiente durante 6 horas. La mezcla se ajusta a un pH de 1 mediante la adición de HCl acuoso 2N, para proporcionar una suspensión blanca. El precipitado se filtra, se lava con agua, y se seca al vacío a 50°C, para dar el compuesto del título como un sólido blanco. MS: 225.0 $[M-H]^+$. ^1H RMN ($CDCl_3$): δ 1.88 (m, 2H), 3.57 (m, 2H), 3.83 (s, 3H), 4.07 (m, 2H), 4.56 (s, br, 1H), 7.06 (dd, 1H), 7.46 (d, 1H)=, 7.57 (dd, 1H), 12.7 (s, br, 1H) ppm.

Ácido 4-metoxi-3-(4-metoxi-butil)-benzoico



280

a. 4-metoxi-3-(4-metoxi-butil)-benzaldehído.

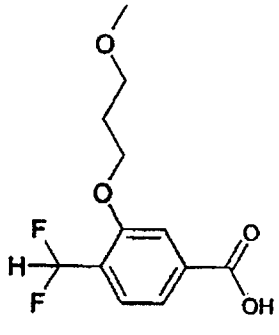
A una solución de 4-bromo-1-metoxi-2-(4-metoxi-butil)-benceno (8.10 gramos, 29.7 milimoles; descrito en la Patente Europea Número EP0678 503 B1) en tetrahidrofurano absoluto (170 mililitros), enfriada a -78°C, se le agrega por goteo durante 30 minutos y bajo una atmósfera de argón, una solución 1.6M de N-butil-litio en hexano (20.4 mililitros, 32.6 milimoles). Después de agitar durante 5 minutos, se agrega una mezcla de dimetil-formamida (5.03 mililitros, 65.2 milimoles) en tetrahidrofurano (20 mililitros) durante 30 minutos a -78°C. La agitación se continúa durante 15 minutos a -78°C, y la mezcla de reacción se calienta gradualmente y se agita durante 1 hora adicional a temperatura ambiente antes de apagar con HCl 1N. La capa acuosa se extrae con dietil-éter (200 mililitros, tres veces), los orgánicos combinados se secan (Na_2SO_4), y se concentran. La purificación mediante cromatografía por evaporación instantánea sobre gel de sílice (hexano/AcOEt, 4:1) da el compuesto del título como un aceite amarillento. TLC, R_f (hexano/AcOEt, 4:1) = 0.27. MS: 223.2 $[M+H]^+$. ^1H RMN ($CDCl_3$): 1.6-1.74 (m, 4H), 2.70 (t, 2H), 3.37 (s, 3H), 3.43 (t, 2H), 3.96 (s, 3H), 6.99 (dd, 1H), 7.73 (d, 1H), 7.76 (dd, 1H), 9.70 (s, 1H) ppm.

b. Ácido 4-metoxi-3-(4-metoxi-butil)-benzoico.

A una solución agitada de 4-metoxi-3-(4-metoxi-butil)-benzaldehído (300 miligramos, 1.35 milimoles) y ácido sulfámico

(176 miligramos, 1.81 milimoles) en ácido acético al 80 por ciento (2.3 mililitros), se le agrega por goteo una solución de $NaClO_2$ al 80 por ciento (127 miligramos, 1.40 milimoles; disuelto en 170 microlitros de H_2O) en agua (0.65mililitros) durante 5 minutos, y manteniendo la temperatura a 18-20°C. La agitación de la pasta amarilla se continúa durante 3 horas a 20°C, antes de agregar otra alícuota de $NaClO_2$ al 80 por ciento (151 miligramos, 1.67 milimoles; disuelto en 205 microlitros de H_2O), disuelta en agua (0.8 mililitros), y ácido sulfámico (130 miligramos, 1.34 milimoles) en ácido acético acuoso al 80 por ciento. Después de agitar durante la noche, la mezcla de reacción se diluye mediante la adición de agua (2.3 mililitros), la suspensión resultante se agita durante 30 minutos, y se filtra. El precipitado se seca para dar el producto del título como un sólido blanco. TLC, R_f (CH_2Cl_2/MeOH, 98:2) = 0.5 MS: 239.0 $[M+H]^+$. ^1H RMN (CD_3OD): δ 1.55 - 1.7 (m, 4H), 2.65 (t, 2H), 3.31 (s, 3H), 3.41 (t, 2H), 3.89 (s, 3H), 4.87 (s, 1H + D_2O), 6.98 (m, 1H), 7.78 (s, 1H), 7.87 (m, 1H) ppm.

Ácido 4-difluoro-metil-3-(3-metoxi-propoxi)-benzoico



a. 3-metoxi-propil-éster del ácido 4-metil-bencen-sulfínico.

Se agrega lentamente cloruro de toluen-4-sulfonilo (25.4 gramos, 133.2 milimoles) a una solución de 3-metoxi-1-propanol (8.49 mililitros, 88.8 milimoles) y trietil-amina (14.8 mililitros, 106.5 milimoles) en CH_2Cl_2 (80 mililitros) a 0°C. Luego la mezcla de reacción se deja calentar a temperatura ambiente, y se agita durante otras 16 horas. El solvente se evapora, se agrega agua, y la mezcla se extrae con CH_2Cl_2. El secado (Na_2SO_4) de los extractos orgánicos combinados, la filtración, y la evaporación de los solventes, proporcionan el producto crudo, el cual se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente: ciclohexano/AcOEt, 5:1), para dar el producto deseado. MS (LC-MS): 262.1 $[M+18]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.12 minutos.

b. 3-metoxi-propil-éster del ácido 4-formil-3-(3-metoxi-propoxi)-benzoico.

Una mezcla del ácido 4-formil-3-hidroxi-benzoico (1.5 gramos, 8.8 milimoles), 3-metoxi-propil-éster del ácido 4-metil-bencen-sulfínico (4.5 gramos, 18.4 milimoles), di-isopropil-etil-amina (3.4 mililitros, 19.3 milimoles), y NaI (2.63 gramos, 17.5 milimoles) en dimetil-formamida (20 mililitros), se agita a 80°C durante 60 horas, y a 130°C durante otras 5 horas. El solvente se

retira parcialmente bajo presión reducida, se agrega agua, y la mezcla se extrae con acetato de etilo. El lavado (salmuera) y el secado (Na_2SO_4) de los extractos orgánicos combinados, la filtración y la evaporación del solvente, proporcionan el producto crudo. El producto deseado se obtiene mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente: ciclohexano/AcOEt, 3:1) MS (LC-MS): 311.1 $[M+H]^+$; t_R (columna C18 Zorbax SB, del 10 al 95 por ciento de CH_3CN/H_2O/0.8 minutos, 95 por ciento de CH_3CN/H_2O, 0.7 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 1.20 minutos.

c. 3-metoxi-propil-éster del ácido 4-difluoro-metil-3-(3-metoxi-propoxi)-benzoico.

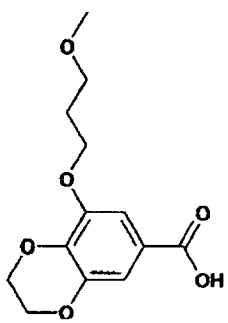
Se agrega lentamente DEOXO-FLÚOR (2.8 mililitros, 15.0 milimoles) a una solución de 3-metoxi-propil-éster del ácido 4-formil-3-(3-metoxi-propoxi)-benzoico (1.81 gramos, 5.8 milimoles) en CH_2Cl_2 (15 mililitros) a 0°C bajo Ar. Luego la mezcla de reacción se agita a temperatura ambiente durante 4.5 horas, se vuelve a enfriar a 0°C antes de agregar etanol (7 mililitros). Entonces la mezcla se agita a temperatura ambiente durante otras 16 horas. El solvente se retira bajo presión reducida, y el producto crudo se purifica mediante cromatografía por evaporación sobre gel de sílice (eluyente: ciclohexano/AcOEt, 3:1), para proporcionar el compuesto del título. MS (LC-MS): 333.1 $[M+H]^+$; t_R (columna C18 Zorbax SB, del 10 al 95 por ciento de CH_3CN/H_2O/0.8 minutos,

95 por ciento de CH_3CN/H_2O, 0.7 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 1.26 minutos.

d. Ácido 4-difluoro-metil-3-(3-metoxi-propoxi)-benzoico.

Se agrega lentamente KOH acuoso 1N (6.7 mililitros, 6.7 milimoles) a una solución de 3-metoxi-propil-éster del ácido 4-difluoro-metil-3-(3-metoxi-propoxi)-benzoico (1.48 gramos, 4.45 milimoles) en MeOH (5 mililitros), y la mezcla de reacción se agita a temperatura ambiente durante 60 horas. Para el procesamiento, la mezcla se concentra bajo presión reducida, el residuo se recupera en HCl 2N (hasta que se obtenga un pH = 1), y se extrae con acetato de etilo. Los extractos orgánicos combinados se lavan con salmuera, se secan (Na_2SO_4), se filtran, y el solvente se evapora para dar el compuesto del título. MS (LC-MS): 259.1 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 4.89 minutos.

Ácido 8-(3-metoxi-propoxi)-2,3-dihidro-benzo-[1,4]-dioxin-6-carboxílico



a. Etil-éster del ácido 8-hidroxi-2,3-dihidro-benzo-[1,4]-dioxin-6-carboxílico.

A una solución del etil-éster del ácido 3,4,5-trihidroxi-benzoico (5.00 gramos, 24.2 milimoles) en dimetil-formamida (70 mililitros), se le agregan 1,2-dibromo-etano (2.13 mililitros, 24.2 milimoles) y $CsCO_3$ (16.9 gramos, 50.9 milimoles), y la mezcla se agita durante la noche a temperatura ambiente, y durante 5 horas a 60°C. El procesamiento de extracción con dietil-éter, el lavado de la fase orgánica con salmuera, y la evaporación, dan el producto crudo como un aceite color café, el cual se purifica mediante cromatografía en gel de sílice (hexano/AcOEt, 3:2). El compuesto del título se obtiene como un sólido blanco. TLC, R_f (hexano/AcOEt, 1:1) = 0.27. MS: 223.0 $[M+H]^+$. ^1H RMN ($CDCl_3$): δ 1.40 (t, 3H), 4.3-4.42 (m, 6H), 5.45 (s, 1H), 7.23 (s, 1H), 7.29 (s, 1H) ppm.

b. Etil-éster del ácido 8-(3-metoxi-propoxi)-2,3-dihidro-benzo-[1,4]-dioxin-6-carboxílico.

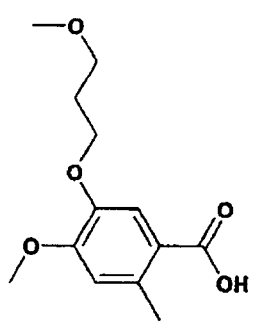
La mezcla del etil-éster del ácido 8-hidroxi-2,3-dihidro-benzo-[1,4]-dioxin-6-carboxílico (1.65 gramos, 7.36 milimoles), 1-bromo-3-metoxi-propano (1.38 gramos, 8.83 milimoles), y K_2CO_3 anhidro (1.53 gramos, 11.0 milimoles) en acetona (40 mililitros) se pone a reflujo durante la noche. Después de enfriar a temperatura ambiente, la mezcla se vierte en agua helada, y se extrae con AcOEt. La capa orgánica se lava con salmuera, se seca (Na_2SO_4), y se concentra. La purificación mediante cromatografía por

evaporación instantánea sobre gel de sílice (hexano/AcOEt, 3:1), produce el compuesto del título como un sólido blanco. TLC, R_f (hexano/AcOEt, 1:1) = 0.32. MS: 297.0 $[M+H]^+$. ^1H RMN ($CDCl_3$): δ 1.41 (t, 3H), 2.16 (m, 2H), 3.40 (s, 3H), 3.61 (m, 2H), 4.20 (m, 2H), 4.31 (m, 2H), 4.35 - 4.45 (m, 4H), 7.27 (d, 1H), 7.31 (d, 1H) ppm.

c. Ácido 8-(3-metoxi-propoxi)-2,3-dihidro-benzo-[1,4]-dioxin-6-carboxílico.

La mezcla del etil-éster del ácido 8-(3-metoxi-propoxi)-2,3-dihidro-benzo-[1,4]-dioxin-6-carboxílico (1.85 gramos, 6.24 milimoles) en dioxano (10 mililitros) y NaOH 2N (5.0 mililitros), se agita a 60°C durante 1 hora, y luego se enfría a temperatura ambiente y se acidifica (pH de 1) con HCl 2N. Los volátiles se retiran bajo presión reducida para proporcionar una suspensión. El precipitado se filtra, se lava con agua helada, y se seca al vacío durante la noche para dar el producto del título como un sólido blanco. TLC, R_f (hexano/AcOEt, 2:1 + 1 por ciento de AcOH) = 0.07. MS: 267.0 $[M-H]^+$. ^1H RMN (DMSO-d_6): δ 1.96 (m, 2H), 3.26 (s, 3H), 3.48 (m, 2H), 4.05 (m, 2H), 4.27 (m, 2H), 4.31 (m, 2H), 7.07 (d, 1H), 7.11 (d, 1H), 12.8 (s, br, 1H) ppm.

Ácido 4-metoxi-5-(3-metoxi-propoxi)-2-metil-benzoico



a. 2-metoxi-1-(3-metoxi-propoxi)-4-metil-benceno.

Una solución agitada de 2-metoxi-4-metil-fenol (5.00 gramos, 36.2 milimoles), 1-bromo-3-metoxi-propano (7.06 gramos, 45.2 milimoles), y K_2CO_3 anhidro (7.50 gramos, 64.3 milimoles), se pone a reflujo durante la noche. Después de enfriarse, los volátiles se retiran bajo presión reducida, el residuo se recupera en agua, y se extrae con AcOEt. Los orgánicos combinados se lavan con salmuera, se secan (NA_2SO_4), y se concentran. Después de la cromatografía en gel de sílice (hexano/AcOEt, 3:1), se obtiene el compuesto del título como un líquido incoloro. TLC, R_f (hexano/AcOEt, 2:1) = 0.34. MS: 211.0 $[M+H]^+$. ^1H RMN ($CDCl_3$): δ 2.13 (m, 2H), 2.33 (s, 3H), 3.38 (s, 3H), 3.61 (m, 2H), 3.88 (s, 3H), 4.12 (m, 2H), 6.7-6.85 (m, 3H) ppm.

b. 1-bromo-4-metoxi-5-(3-metoxi-propoxi)-2-metil-benceno.

A una solución 2-metoxi-1-(3-metoxi-propoxi)-4-metil-benceno (2.00 gramos, 9.51 milimoles) en MeCN (30 mililitros) se agrega N-bromo-succinimida (1.96 gramos, 10.5 milimoles) a temperatura ambiente. La agitación se continúa durante 2 horas, seguida por la evaporación del solvente. El compuesto del título se obtiene después de la cromatografía por evaporación instantánea sobre gel de sílice (hexano/AcOEt, 6:1) como un aceite. MS: 289.0/291.0 $[M]^+$; t_R (HPLC, columna Nucleosil C18 HD, del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1 mililitro/minuto): 5.04 minutos. ^1H RMN

($CDCl_3$): δ 2.13 (m, 2H); 2.36 (s, 3H), 3.39 (s, 3H), 3.58 (m, 2H), 3.87 (s, 3H), 4.12 (m, 2H), 6.77 (s, 1H), 7.08 (s, 1H) ppm.

c. 4-metoxi-5-(3-metoxi-propoxi)-2-metil-benzaldehído.

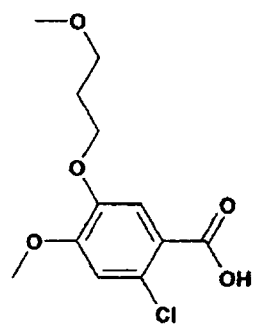
A una solución de 1-bromo-4-metoxi-5-(3-metoxi-propoxi)-2-metil-benceno (2.50 gramos, 8.65 milimoles) en tetrahidrofurano (25 mililitros), enfriada a -70°C, se le agrega una solución 1.6M de n-butil-litio en hexano (5.94 mililitros, 9.51 milimoles). Después de 30 minutos, se agrega dimetil-formamida (1.05 mililitros, 13.0 milimoles), y se continúa la agitación durante la noche, mientras que la mezcla de reacción se calienta gradualmente a temperatura ambiente. El apagado con HCl acuoso 1N helado es seguido por extracción con dietil-éter. Las capas orgánicas combinadas se lavan con salmuera, se secan (Na_2SO_4), y se concentran. La purificación mediante cromatografía por evaporación instantánea sobre gel de sílice (hexano/AcOEt, 7:2), da el compuesto del título como un aceite. TLC, R_f (hexano/AcOEt, 1:1) = 0.29. MS: 239.2 $[M+H]^+$. ^1H RMN ($CDCl_3$): δ 2.16 (m, 2H), 2.66 (s, 3H), 3.39 (s, 3H), 3.60 (m, 2H), 3.97 (s, 3H), 4.16 (m, 2H), 6.73 (s, 1H), 7.40 (s, 1H), 10.2 (s, 1H) ppm.

d. Ácido 4-metoxi-5-(3-metoxi-propoxi)-2-metil-benzoico.

A una solución de 4-metoxi-5-(3-metoxi-propoxi)-2-metil-benzaldehído (1.25 gramos, 5.25 milimoles) en una mezcla de 3:1 de terbutanol/CH_2Cl_2 (60 mililitros), se le agrega 2-metil-2-buteno (25.0 mililitros), seguido por la adición por goteo de una solución de $NaClO_2$ (5.81 graos, 51.4 milimoles) y NaH_2PO_4 (4.07 gramos,

33.6 milimoles) en agua (45 mililitros) durante 15 minutos a temperatura ambiente, y se continúa la agitación durante la noche. La mezcla de reacción se vierte en hielo/solución acuosa saturada de $NaHCO_3$, la fase de agua se lava con AcOEt, luego se acidifica, y se extrae con AcOEt. Los orgánicos combinados se lavan con salmuera, se secan (Na_2SO_4), y se concentran, para dar un sólido amarillo. El producto crudo se agita durante 30 minutos en una mezcla de 95:5 de hexano/di-isopropil-éter (25 mililitros), el precipitado se filtra, se lava con una mezcla de 95:5 de hexano/di-isopropil-éter, y se seca, para dar el compuesto del título como un sólido amarillento. MS: 253.0 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18HD, del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1 mililitro/minuto): 3.23 minutos. ^1H RMN ($CDCl_3$): δ 1.96 (m, 2H), 2.51 (s, 3H), 3.27 (s, 3H), 3.48 (m, 2H), 3.84 (s, 3H), 4.00 (m, 2H), 6.89 (s, 1H), 7.41 (s, 1H) ppm.

Ácido 2-cloro-4-metoxi-5-(3-metoxi-propoxi)-benzoico



a. 2-cloro-5-hidroxi-4-metoxi-benzaldehído.

El 2-cloro-4,5-dimetoxi-benzaldehído (5.00 gramos, 24.9 milimoles; comercialmente disponible en Akos Consulting) se disuelve a temperatura ambiente en H_2SO_4 concentrado (23 mililitros; Riedel) a temperatura ambiente. La mezcla profundamente coloreada se calienta a 65°C durante la noche con agitación, y después de enfriarse, se vierte con precaución en agua helada conteniendo 38 gramos de NaOH sólido (pH de 14). La fase de agua se lava dos veces con AcOEt, y luego se ajusta a un pH de 1 mediante la adición de HCl al 37 por ciento con enfriamiento con hielo para formar una suspensión blanca. La extracción con AcOEt, el secado de los orgánicos sobre $MgSO_4$, y la evaporación, dan el producto crudo en una mezcla con material de inicio sin reaccionar. El compuesto del título se obtiene después de la cromatografía en gel de sílice (gradiente de hexano/AcOEt de 3:1 a 1:1) como un sólido blanco. TLC, R_f (hexano/AcOEt, 1:1) = 0.35. MS: 187.0 $[M+H]^+$. ^1H RMN (DMSO-d_6): δ 3.41 (s, 3H), 7.14 (s, 1H), 7.45 (s, 1H), 9.83 (s, 1H), 10.2 (s, 1H) ppm.

b. 2-cloro-4-metoxi-5-(3-metoxi-propoxi)-benzaldehído.

Una mezcla de 2-cloro-5-hidroxi-4-metoxi-benzaldehído crudo (1.79 gramos, 8.15 milimoles), 1-bromo-3-metoxi-propano (1.53 gramos, 9.79 milimoles), y K_2CO_3 anhidro (1.69 gramos, 12.2 milimoles) en MeCN (30 mililitros) se pone a reflujo durante la

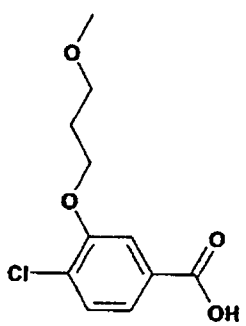
noche. Se agrega agua helada a la mezcla, seguida por extracción con AcOEt. Los orgánicos combinados se lavan con salmuera, se secan (Na_2SO_4), y se concentran. El compuesto del título se obtiene después de la purificación mediante RP-HPLC sobre una columna PrepC_{18} OBD (dimensiones: 30 x 100 milímetros; tamaño de partículas de 5 micras, SunFire Ltd.), y utilizando un gradiente del 95 al 100 por ciento de MeCN/H_2O, 5:95 (conteniendo ácido trifluoro-acético al 0.1 por ciento) hasta MeCN/H_2O, 95:5 (conteniendo ácido trifluoro-acético al 0.1 por ciento) durante 20 minutos, como un sólido. TLC, R_f (hexano/AcOEt, 1:1) = 0.42. MS: 259.0 $[M+H]^+$; t_R (HPLC, columna Nucleosil CD18HD, del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1 mililitro/minuto): 4.15 minutos. ^1H RMN ($CDCl_3$): δ 2.15 (m, 2H), 3.39 (s, 3H), 3.59 (m, 2H), 3.99 (s, 3H), 4.19 (m, 2H), 6.91 (s, 1H), 7.45 (s, 1H), 10.4 (s, 1H) ppm.

c. Ácido 2-cloro-4-metoxi-5-(3-metoxi-propoxi)-benzoico.

A una solución de 2-cloro-4-metoxi-5-(3-metoxi-propoxi)-benzaldehído (1.08 gramos, 3.55 milimoles) en una mezcla de 3:1 de terbutanol/CH_2Cl_2 (20 mililitros), se le agrega 2-metil-2-buteno (0.74 gramos, 5.32 milimoles), seguido por la adición por goteo de una solución de $NaClO_2$ (0.67 gramos, 7.10 milimoles) y NaH_2PO_4 (0.67 gramos, 4.26 milimoles) en agua (14 mililitros) durante 15 minutos a temperatura ambiente, y se continúa la agitación durante

la noche. La mezcla de reacción se vierte en hielo/solución acuosa saturada de $NaHCO_3$, La fase de agua se lava con AcOEt. La capa acuosa helada se acidifica con HCl al 37 por ciento, para formar un precipitado blanco, el cual se filtra, se lava con agua helada, y se seca al vacío. El compuesto se obtiene como un sólido blanco. MS: 273.0 $[M-H]^{+`}$; t_R (HPLC, columna Nucleosil CD18HD, del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1 mililitro/minuto): 3.25 minutos. ^1H RMN ($CDCl_3$): δ 1.96 (m, 2H), 3.25 (s, 3H), 3.47 (m, 2H), 3.85 (s, 3H), 4.03 (m, 2H), 7.10 (s, 1H), 7.39 (s, 1H) ppm.

Ácido 4-cloro-3-(3-metoxi-propoxi)-benzoico



a. 3-metoxi-propil-éster del ácido 4-cloro-3-(3-metoxi-propoxi)-benzoico.

Una mezcla del ácido 4-cloro-3-hidroxi-benzoico (4.02 gramos, 23.3 milimoles; comercialmente disponible en Frinton Laboratories), 1-bromo-3-metoxi-propano (8.73 gramos, 55.9 milimoles), y K_2CO_3 anhidro (9.66 gramos, 69.9 milimoles) en

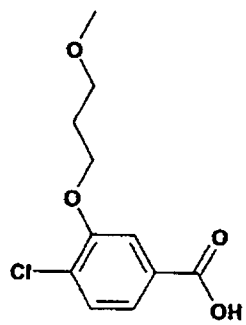
MeCN (80 mililitros), se pone a reflujo durante la noche. Se agrega una cantidad adicional de 1-bromo-3-metoxi-propano (1.82 gramos, 0.5 equivalentes) bajo condiciones de reflujo. Después de 2 horas, la mezcla se vierte en agua helada, y se extrae con AcOEt. Los orgánicos combinados se lavan con salmuera, se secan (Na_2SO_4), y se concentran. La cromatografía por evaporación instantánea sobre gel de sílice (hexano/AcOEt, 7:2) proporciona el compuesto del título como un aceite. TLC, R_f (hexano/AcOEt, 3:1) 0.17. MS: 317.2 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18HD, del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoroacético al 0.1 por ciento, flujo: 1 mililitro/minuto): 5.13 minutos. ^1H RMN ($CDCl_3$): δ 2.06 (m, 2H), 2.16 (m, 2H), 3.40 (s, 6H), 3.57 (m, 2H), 3.65 (m, 2H), 4.23 (m, 2H), 4.45 (m, 2H), 7.45 (m, 1H), 7.61 (m, 1H), 7.64 (s, 1H) ppm.

b. Ácido 4-cloro-3-(3-metoxi-propoxi)-benzoico.

Una solución del 3-metoxi-propil-éster del ácido 4-cloro-3-(3-metoxi-propoxi)-benzoico (1.58 gramos, 4.99 milimoles) en NaOH 2N acuoso (3.23 mililitros, 6.48 milimoles) y dioxano (10 mililitros), se agita a temperatura ambiente durante 3.5 horas. La mezcla se acidifica mediante la adición de HCl 2N, los volátiles se retiran mediante evaporación, y la suspensión obtenida se filtra. El precipitado se lava con agua helada, y se seca al vacío, para dar el compuesto del título como un sólido blanco. MS: 243.0 $[M-H]^+$; t_R

(HPLC, columna Nucleosil C18HD, del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1 mililitro/minuto): 3.93 minutos. ^1H RMN (DMSO-d_6): δ 2.00 (m, 2H), 3.27 (s, 3H), 3.34 (s, br, 1H), 3.53 (m, 2H), 4.19 (m, 2H), 7.5-7.6 (m, 3H) ppm.

Ácido 3-cloro-5-(3-metoxi-propoxi)-benzoico



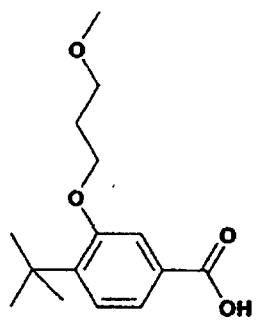
a. 3-metoxi-propil-éster del ácido 3-cloro-5-(3-metoxi-propoxi)-benzoico.

El compuesto del título se obtiene a partir del ácido 3-cloro-5-hidroxi-benzoico (1.96 gramos, 11.4 milimoles; comercialmente disponible en J&W Pharm. Lab), 1-bromo-3-metoxi-propano (4.25 gramos, 27.3 milimoles), y K_2CO_3 anhidro (4.71 gramos, 34.1 milimoles), como se describe anteriormente para el regioisómero de 4-cloro, como un aceite. TLC, R_f (hexano/AcOEt, 3:1) = 0.21. MS: 317.0 $[M+H]^+$. ^1H RMN ($CDCl_3$): δ 2.07 (m, 2H), 2.10 (m, 2H), 3.39 (s, 3H), 3.41 (s, 3H), 3.56 (m, 2H), 3.59 (m, 2H), 4.13 (m, 2H), 4.45 (m, 2H), 7.13 (m, 1H), 7.49 (m, 1H), 7.63 (m, 1H) ppm.

b. Ácido 3-cloro-5-(3-metoxi-propoxi)-benzoico.

El compuesto del título se obtiene a partir del 3-metoxi-propil-éster del ácido 3-cloro-5-(3-metoxi-propoxi)-benzoico (1.70 gramos, 5.37 milimoles), disuelto en dioxano (10 mililitros), mediante hidrólisis con NaOH acuoso 2N, como un sólido blanco. MS: 243.0 $[M-H]^+$; t_R (HPLC, columna Nucleosil C18HD, del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1 mililitro/minuto): 4.04 minutos. ^1H RMN (DMSO-d_6): δ 1.96 (m, 2H), 3.25 (s, 3H), 3.36 (s, br, 1H), 3.48 (m, 2H), 4.11 (m, 2H), 7.31 (s, 1H), 7.40 (s, 1H), 7.49 (s, 1H) ppm.

Ácido 4-terbutil-3-(3-metoxi-propoxi)-benzoico



a. Metil-éster del ácido 4-terbutil-3-metoxi-benzoico.

A una solución del ácido 4-terbutil-3-metoxi-benzoico (3.00 gramos, 14.4 milimoles; comercialmente disponible en Apin, 41226B) en MeOH (30 mililitros), se le agrega H_2SO_4 concentrado (3 mililitros), y la mezcla se pone a reflujo durante 5 horas. Después de enfriarse, la mezcla se diluye con agua, se extrae dos

veces con dietil-éter, los orgánicos combinados se secan (Na_2SO_4), y se evaporan a sequedad, para dar el compuesto del título como un aceite amarillento. MS: 223.0 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18HD, del 5 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1 mililitro/minuto): 6.12 minutos. ^1H RMN ($CDCl_3$): δ 1.41 (s, 9H), 3.91 (s, 3H), 3.92 (s, 3H), 7.36 (dd, 1H), 7.54 (d, 1H), 7.60 (dd, 1H) ppm.

b. Metil-éster del ácido 4-terbutil-3-hidroxi-benzoico.

A una solución de tribromuro de boro (3.38 mililitros, 35.1 milimoles) en CH_2Cl_2 (35 mililitros), enfriada a -60°C, se le agrega, bajo una atmósfera de argón, una solución de metil-éster del ácido 4-terbutil-3-metoxi-benzoico (2.60 gramos, 11.7 milimoles) en CH_2Cl_2 (65 mililitros). La reacción se calienta a temperatura ambiente, y se continúa la agitación durante la noche. Se agrega otra alícuota de BBr_3 (1.13 mililitros, 11.7 milimoles), y la mezcla se agita durante 6 horas a temperatura ambiente, antes de apagar mediante la adición cuidadosa de agua. La capa acuosa se extrae con CH_2Cl_2, los orgánicos combinados se lavan con NaOH acuoso 1N, se secan (Na_2SO_4), y se concentran. La purificación mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyentes: CH_2Cl_2 al 100 por ciento, luego CH_2Cl_2/acetona, 97:3), da el compuesto del título como un sólido amarillento. MS: 209.0

$[M+H]^+$; t_R (HPLC, columna Nucleosil C18HD, del 5 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1 mililitro/minuto): 5.37 minutos. ^1H RMN ($CDCl_3$): δ 1.46 (s, 9H), 3.94 (s, 3H), 5.60 (s, 1H), 7.36 (dd, 1H), 7.50 (d, 1H), 7.57 (dd, 1H) ppm.

Las capas acuosas alcalinas obtenidas anteriormente se acidifican con HCl concentrado, se extrae con CH_2Cl_2, los orgánicos se secan (Na_2SO_4), y se evaporan a sequedad, para dar el ácido 4-terbutil-3-hidroxi-benzoico: MS: 193.0 $[M+H]^+$. ^1H RMN (DMSO-d_6): δ 1.37 (s, 9H), 7.26 (m, 1H), 7.33 (m, 1H), 7.40 (m, 1H), 9.71 (s, 1H), 12.7 (s, 1H) ppm.

c. Metil-éster del ácido 4-terbutil-3-(3-metoxi-propoxi)-benzoico.

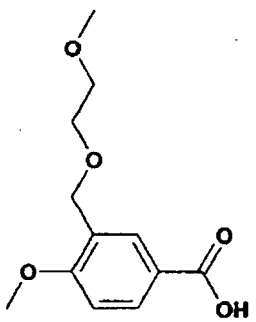
Una mezcla del metil-éster del ácido 4-terbutil-3-hidroxi-benzoico (1.56 gramos, 7.49 milimoles), 3-bromo-propil-metil-éter (1.72 gramos, 11.2 milimoles), y K_2CO_3 anhidro (1.55 gramos, 11.2 milimoles) en MeCN (30 mililitros), se pone a reflujo durante la noche. Después de enfriarse, la mezcla se filtra, el filtrado se diluye con CH_2Cl_2, y los orgánicos se lavan con NaOH 0.5M acuoso, HCl 0.5M acuoso, y agua, se secan (Na_2SO_4), y se concentran. La purificación mediante cromatografía por evaporación instantánea sobre gel de sílice (hexano/AcOEt, 97:3), da el compuesto del título como un aceite incoloro. MS: 281.1

$[M+H]^+$; t_R (HPLC, columna Nucleosil C18HD, del 5 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1 mililitro/minuto): 6.22 minutos. ^1H RMN ($CDCl_3$): δ 1.43 (s, 9H), 2.17 (m, 2H), 3.41 (s, 3H), 3.65 (m, 2H), 3.93 (s, 3H), 4.18 (m, 2H), 7.36 (dd, 1H), 7.96 (d, 1H), 7.60 (dd, 1H) ppm.

d. Ácido 4-terbutil-3-(3-metoxi-propoxi)-benzoico.

El compuesto del título se obtiene mediante la hidrólisis del metil-éster del ácido 4-terbutil-3-(3-metoxi-propoxi)-benzoico (1.60 gramos, 5.14 milimoles), disuelto en EtOH (15 mililitros), en la presencia de NaOH 2N acuoso (3.85 mililitros, 7.70 milimoles) como un polvo grisáceo. MS: 284.1 $[M+H_2O]^+$; t_R (HPLC, columna Nucleosil C18HD, del 5 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1 mililitro/minuto): 5.42 minutos. ^1H RMN (DMSO-d_6): δ 1.36 (s, 9H), 2.04 (m, 2H), 3.26 (s, 3H), 3.94 (m, 2H), 4.09 (m, 2H), 7.34 (m, 1H), 7.49 (s, 1H), 7.48 (m, 1H), 12.8 (s, br, 1H) ppm.

Ácido 4-metoxi-3-(2-metoxi-etoxi-metil)-benzoico



a. (5-bromo-2-metoxi-fenil)-metanol.

A una suspensión de 5-bromo-2-metoxi-benzaldehído (7.00 gramos, 32.2 milimoles) en MeOH (40 mililitros), enfriada a 0-5°C, se le agrega $NaBH_4$ (1.40 gramos, 35.4 milimoles). Después de agitar durante 1 hora, la mezcla se vierte en agua helada, seguido por extracción con AcOEt. Los orgánicos combinados se lavan con salmuera, se secan (Na_2SO_4), y se concentran, para dar el producto del título como un sólido grisáceo. TLC, R_f (hexano/AcOEt, 3:1) = 0.19. ^1H RMN ($CDCl_3$): δ 2.24 (m, 2H), 3.88 (s, 3H), 4.68 (d, 2H), 6.79 (dd, 1H), 7.41 (dd, 1H), 7.45 (d, 1H) ppm.

b. 4-bromo-1-metoxi-2-(2-metoxi-etoxi-metil)-benceno.

A una solución del (5-bromo-2-metoxi-fenil)-metanol (3.38 gramos, 14.8 milimoles) y 2-bromo-etil-metil-éter (2.06 gramos, 14.8 milimoles) en dimetil-formamida (30 mililitros), se le agrega NaH (dispersión al 55 por ciento en aceite; 1.36 gramos, 31.1 milimoles) en tres porciones a temperatura ambiente, seguido por agitación durante la noche. La mezcla se vierte en HCl 2N acuoso helado, la fase de agua se extrae con dietil-éter, la fase orgánica combinada se lava con salmuera, se seca (Na_2SO_4), y se concentra. La purificación mediante cromatografía por evaporación instantánea (hexano/AcOEt, 1:1), da el compuesto del título como un líquido. TLC, R_f (hexano/AcOEt, 1:1) = 0.44. ^1H RMN ($CDCl_3$): δ 3.45 (s, 3H), 3.64 (m, 2H), 3.71 (m, 2H), 3.83 (s, 3H), 4.60 (s, 2H), 6.76 (d, 1H), 7.37 (dd, 1H), 7.56 (d, 1H) ppm.

c. Etil-éster del ácido 4-metoxi-3-(2-metoxi-etoxi-metil)-benzoico.

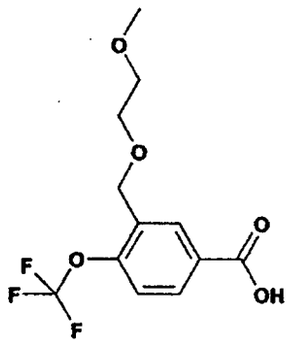
A una solución del 4-bromo-1-metoxi-2-(2-metoxi-etoxi-metil)-benceno (2.88 gramos, 10.5 milimoles) en tetrahidrofurano absoluto (30 mililitros), se le agrega, a -70°C, una solución 1.6N de N-butil-litio en hexano (7.20 mililitros, 11.5 milimoles) con agitación. Después de 40 minutos, se agrega cloroformato de etilo (1.14 gramos, 10.5 milimoles), y la mezcla se agita durante la noche, mientras que se calienta gradualmente a temperatura ambiente. La mezcla se vierte en HCl acuoso 2N, se extrae con CH_2Cl_2, las capas orgánicas se secan (Na_2SO_4), y se concentran. El producto crudo se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (hexano/AcOEt, 2:1), para dar el compuesto del título como un líquido. TLC, R_f (hexano/AcOEt, 1:1) = 0.13.

d. Ácido 4-metoxi-3-(2-metoxi-etoxi-metil)-benzoico.

Una solución del etil-éster del ácido 4-metoxi-3-(2-metoxi-etoxi-metil)-benzoico (0.87 gramos, 3.24 milimoles) en una mezcla de 1:1 de tetrahidrofurano y NaOH 4N (10 mililitros), se agita a 50°C durante la noche. Después de enfriarse, los volátiles se retiran a presión reducida, la fase acuosa restante se acidifica a un pH de 1 mediante la adición por goteo de HCl al 37 por ciento, y la suspensión resultante se filtra. El precipitado se lava con agua, se seca durante la noche al vacío para dar el compuesto del

título. TLC, R_f (hexano/AcOEt, 1:1) = 0.07. MS: 239.0 $[M-H]^+$; t_R (HPLC, columna Nucleosil C18HD, del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1 mililitro/minuto): 2.71 minutos. ^1H RMN (DMSO-d_6): δ 3.29 (s, 3H), 3.52 (m, 2H), 3.64 (m, 2H), 3.88 (s, 3H), 4.51 (s, 2H), 7.10 (m, 1H), 7.90 (m, 1H), 7.94 (m, 1H), 12.6 (s, br, 1H) ppm.

Ácido 3-(2-metoxi-etoxi-metil)-4-trifluoro-metoxi-benzoico



a. (5-bromo-2-trifluoro-metoxi-fenil)-metanol.

A una solución del ácido 5-bromo-2-trifluoro-metoxi-benzoico (2.00 gramos, 7.02 milimoles, comercialmente disponible en Rare Chemicals, AL BE 0523) y NEt_3 (1.47 mililitros, 10.5 milimoles) en tetrahidrofurano (50 mililitros), enfriada a -15°C y bajo una atmósfera de argón, se le agrega por goteo cloroformato de isobutilo (1.15 mililitros, 8.77 milimoles). La mezcla se agita durante 1 hora después de calentar a temperatura ambiente, seguido por la adición de AcOEt (20 mililitros). La capa orgánica subsecuentemente se lava con HCl 0.5M (20 mililitros), una

solución acuosa saturada de $NaHCO_3$ (20 mililitros), y agua (20 mililitros), y luego se seca sobre Na_2SO_4 y se concentra para dar el intermediario de anhídrido mixto.

A una solución del anhídrido mixto obtenido anteriormente (1.50 gramos, 3.90 milimoles) en tetrahidrofurano (40 mililitros), enfriada a 0-5°C, se le agrega por goteo una solución de $LiBH_4$ (0.17 gramos, 7.79 milimoles) en tetrahidrofurano (5 mililitros). Después de calentar a temperatura ambiente, la mezcla de reacción se agita durante la noche, y luego se apaga mediante la adición de NaOH 2N acuoso (30 mililitros). La extracción de la fase de agua con AcOEt, el secado de los orgánicos combinados (Na_2SO_4), y la evaporación a sequedad, dan el compuesto del título; t_R (HPLC, columna Nucleosil C18HD, del 5 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1 mililitro/minuto): 5.04 minutos. ^1H RMN (DMSO-d_6): δ 4.56 (d, 2H), 5.51 (t, 1H), 7.31 (dd, 1H), 7.59 (dd, 1H), 7.73 (d, 1H) ppm.

b. 4-bromo-2-(2-metoxi-etoxi-metil)-1-trifluoro-metoxi-benceno.

En un matraz de tres cuellos bajo argón, una dispersión al 50-65 por ciento de NaH en aceite (0.097 gramos, 2.44 milimoles) se lava con pentano normal, los orgánicos se retiran, y se agrega dimetil-formamida (10 mililitros). La mezcla se enfría a 0-5°C, y se agrega por goteo una solución de (5-bromo-2-trifluoro-metoxi-

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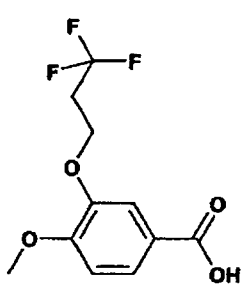
fenil)-metanol (0.60 gramos, 2.21 milimoles) en dimetil-formamida (3.0 mililitros). Después de calentar a temperatura ambiente, se continúa la agitación durante 1 hora, antes de agregar esta mezcla a una solución de 2-bromo-etil-metil-éter (0.312 mililitros, 3.32 milimoles) en dimetil-formamida (3 mililitros). Después de 4 horas a temperatura ambiente, la reacción todavía está incompleta mediante TLC. Se agregan otra alícuota de NaH (1 equivalente; dispersión en aceite lavada con pentano) y 2-bromo-etil-metil-éter (0.312 mililitros, 3.32 milimoles), seguido por agitación durante 18 horas a temperatura ambiente. La mezcla se vierte en agua helada, y se extrae con AcOEt, los orgánicos combinados se secan (Na_2SO_4), y se evaporan a sequedad, para dar el compuesto del título como un aceite amarillento. MS: 346.0/348.0 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18HD, del 5 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1 mililitro/minuto): 5.80 minutos. ^1H RMN ($CDCl_3$): δ 3.49 (s, 3H), 3.64 (m, 2H), 3.72 (m, 2H), 4.69 (s, 2H), 7.13 (dd, 1H), 7.46 (dd, 1H), 7.77 (d, 1H) ppm.

c. Ácido 3-(2-metoxi-etoxi-metil)-4-trifluoro-metoxi-benzoico.

A una solución de 4-bromo-2-(2-metoxi-etoxi-metil)-1-trifluoro-metoxi-benceno (0.28 gramos, 0.85 milimoles) en dietil-éter absoluto (2.0 mililitros), enfriada a -70°C, se le agrega por goteo bajo una atmósfera de argón, una solución 1.7M de terbutil-

litio en pentano (0.50 mililitros, 0.85 milimoles). Después de agitar durante 30 minutos, se burbujea gas de CO_2 en la solución durante 2 minutos, seguido por agitación de la solución amarilla a -70°C durante 30 minutos adicionales. La reacción se apaga mediante la adición de una solución acuosa saturada de NH_4Cl (2 mililitros). La capa acuosa básica se lava con AcOEt, y, después de la acidificación hasta un pH de 1, se extrae dos veces con AcOEt. Los orgánicos combinados se secan sobre Na_2SO_4, y se evaporan a sequedad, para dar el compuesto del título como un aceite incoloro. MS: 293.0. $[M-H]^+$; t_R (HPLC, columna Nucleosil C18HD, del 5 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1 mililitro/minuto): 4.62 minutos. ^1H RMN ($CDCl_3$): δ 3.46 (s, 3H), 3.67 (m, 2H), 3.76 (m, 2H), 4.71 (s, 2H), 7.35 (dd, 1H), 8.09 (dd, 1H), 8.35 (dd, 1H) ppm.

Ácido 4-metoxi-3-(3,3,3-trifluoro-propoxi)-benzoico



a. Etil-éster del ácido 4-metoxi-3-(3,3,3-trifluoro-propoxi)-benzoico.

La mezcla del etil-éster del ácido 3-hidroxi-4-metoxi-

benzoico (1.75 gramos, 8.92 milimoles), 3,3,3-trifluoro-propil-éster del ácido metansulfónico (2.06 gramos, 10.7 milimoles), y K_2CO_3 anhidro (2.49 gramos, 17.8 milimoles) en acetona (20 mililitros), se calienta con agitación a la temperatura de reflujo durante la noche. Después de enfriarse, la mezcla se diluye con AcOEt, seguido por lavado de la fase orgánica con NaOH acuoso 2N y salmuera. La capa orgánica se seca sobre Na_2SO_4 y se evapora, y el producto crudo se purifica mediante cromatografía en gel de sílice (eluyente: hexano/AcOEt, 5:1), para dar el compuesto del título como un aceite. TLC, R_f (hexano/AcOEt, 1:1) = 0.59. MS: 293.0. $[M+H]^+$. ^1H RMN ($CDCl_3$): δ 1.42 (t, 3H), 2.74 (m, 2H), 3.96 (s, 3H), 4.33 (m, 2H), 4.40 (m, 2H), 6.94 (m, 1H), 7.59 (s, 1H), 7.77 (m, 1H) ppm.

b. Ácido 4-metoxi-3-(3,3,3-trifluoro-propoxi)-benzoico.

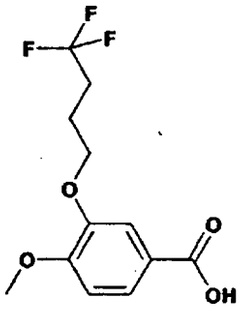
El compuesto del título se obtiene como un sólido blanco a partir del etil-éster del ácido 4-metoxi-3-(3,3,3-trifluoro-propoxi)-benzoico (0.62 gramos, 2.12 milimoles), disuelto en tetrahidrofurano (3.0 mililitros), después de la hidrólisis en la presencia de NaOH 2N (1.6 mililitros) a 60°C durante la noche. La mezcla de reacción helada se acidifica (pH de 1) con HCl al 37 por ciento, para formar un precipitado blanco, el cual se filtra, se lava con agua, y se seca al vacío. TLC, R_f (hexano/AcOEt, 1:1) = 0.17. MS: 263.0 $[M-H]^+$; t_R (HPLC, columna Nucleosil C18HD, del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de

CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1 mililitro/minuto): 3.50 minutos. ^1H RMN ($CDCl_3$): δ 2.81 (m, 2H), 3.85 (s, 3H), 4.25 (m, 2H), 7.10 (dd, 1H), 7.49 (d, 1H), 7.63 (dd, 1H), 12.6 (s, br, 1H) ppm.

El 3,3,3-trifluoro-propil-éster del ácido metan-sulfónico se prepara de acuerdo con el siguiente procedimiento:

A la mezcla de 3,3,3-trifluoro-1-propanol (1.28 gramos, 10.8 milimoles) y NEt_3 (4.53 mililitros, 32.7 milimoles) en CH_2Cl_2 (10 mililitros), se le agrega por goteo a -20°C, metansulfocloruro (1.03 mililitros, 13.1 milimoles). La mezcla se calienta lentamente durante 90 minutos a 5°C con agitación, seguido por la adición de CH_2Cl_2 y el lavado de la capa orgánica con HCl acuoso 2N. Los orgánicos se secan sobre Na_2SO_4 y se concentran al vacío, para dar el producto del título crudo como un líquido amarillento, el cual se utiliza sin mayor purificación. ^1H RMN ($CDCl_3$): δ 2.64 (m, 2H), 3.09 (s, 3H), 4.47 (t, 2H) ppm.

Ácido 4-metoxi-3-(4,4,4-trifluoro-butoxi)-benzoico



a. Etil-éster del ácido 4-metoxi-3-(4,4,4-trifluoro-butoxi)-benzoico.

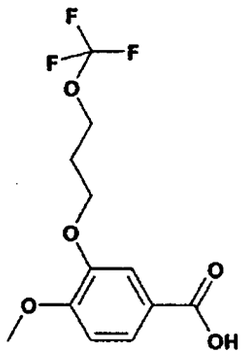
Una suspensión de etil-éster del ácido 3-hidroxi-4-metoxi-benzoico (1.00 gramos, 5.10 milimoles), 1-bromo-4,4,4-trifluoro-butano (1.12 gramos, 5.86 milimoles), y K_2CO_3 anhidro (2.14 gramos, 15.3 milimoles) en MeCN (10 mililitros), se pone a reflujo con agitación durante la noche. Después de enfriarse, la mezcla se filtra, y los filtrados se evaporan a sequedad, para dar el compuesto del título como un sólido blanco. TLC, R_f (hexano/AcOEt, 1:1) = 0.62. MS: 307.0 $[M+H]^+$. ^1H RMN ($CDCl_3$): δ 1.42 (m, 3H), 2.1-2.2 (m, 2H), 2.3-2.45 (m, 2H), 3.95 (s, 3H), 4.14 (m, 2H), 4.39 (m, 2H), 6.93 (dd, 1H), 7.58 (d, 1H), 7.74 (dd, 1H) ppm.

b. Ácido 4-metoxi-3-(4,4,4-trifluoro-butoxi)-benzoico.

Una mezcla del etil-éster del ácido 4-metoxi-3-(4,4,4-trifluoro-butoxi)-benzoico (0.93 gramos, 3.04 milimoles) en tetrahidrofurano (3 mililitros) y NaOH 2N (2.28 mililitros, 4.55 milimoles), se calienta con agitación a 60°C durante la noche. Después de enfriarse, se agrega agua helada, y el pH se ajusta a 1 mediante la adición de HCl al 37 por ciento, para formar un precipitado blanco, el cual se filtra. El compuesto del título se obtiene después del secado como un sólido blanco. TLC, R_f (hexano/AcOEt, 1:1) = 0.17. MS: 277.0 $[M-H]^+$; t_R (HPLC, columna Nucleosil C18HD, del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1

mililitro/minuto): 3.90 minutos. ^{1}H RMN ($CDCl_3$): δ 1.98 (m, 2H), 2.45 (m, 2H), 3.85 (s, 3H), 4.08 (m, 2H), 7.08 (dd, 1H), 7.46 (d, 1H), 7.60 (dd, 1H), 12.7 (s, br, 1H) ppm.

Ácido 4-metoxi-3-(3-trifluoro-metoxi-propoxi)-benzoico



a. S-metil-éster de O-(3-etoxi-propil)-éster del ácido ditiocarbónico.

El compuesto del título se prepara mediante el método descrito en Bull. Chem. Soc. Jpn. (2000), 73, 477f.: A una solución enfriada de 3-etoxi-1-propanol (24.4 gramos, 0.227 moles) en dimetil-formamida (150 mililitros), se le agrega NaH (dispersión al 60 por ciento en aceite (10.0 gramos, 0.250 moles) en porciones durante 1 hora, manteniendo la temperatura de reacción debajo de 5°C. La agitación se continúa durante 5 horas a temperatura ambiente, la mezcla se enfría de 5°C a 10°C, seguido por la adición por goteo de CS_2 (27.5 mililitros, 0.454 moles). La mezcla calienta gradualmente a temperatura ambiente durante la noche, y luego se enfría a <10°C antes de agregar yodo-metano (17.9 mililitros, 0.284 moles). La agitación se continúa durante 18 horas

a temperatura ambiente, luego la mezcla se vierte en HCl acuoso diluido helado, y se extrae con dietil-éter. Las capas orgánicas combinadas se lavan con salmuera, se secan sobre $MgSO_4$, y se concentran, para dar un aceite amarillo. La purificación mediante cromatografía por evaporación sobre gel de sílice (hexano/AcOEt, 20:1) da el compuesto del título como un líquido amarillo. TLC, R_f (hexano/AcOEt, 3:1) = 0.56. ^1H RMN ($CDCl_3$): δ 1.23 (t, 3H), 2.11 (m, 2H), 2.60 (s, 3H), 3.52 (t, 2H), 3.58 (t, 2H), 4.79 (t, 2H) ppm.

b. 1-etoxi-3-trifluoro-metoxi-propano.

Siguiendo el método descrito en Tetrahedron Letters (1992), 33, 4173-4176, una suspensión de 1,3-dibromo-5,5-dimetil-hidantoína (78.5 gramos, 0.266 moles) en CH_2Cl_2 (0.8 litros), se enfría a -70°C, seguido por la adición por goteo de fluoruro de hidrógeno/piridina (99.2 mililitros, 3.82 moles; Fluka No. 47586). A esta mezcla se le agrega entonces lentamente una solución de S-metil-éster de O-(3-etoxi-propil)-éster del ácido ditiocarbónico (23.0 gramos, 0.089 moles) en CH_2Cl_2 (200 mililitros). La mezcla de reacción amarilla se calienta a temperatura ambiente durante 3.5 horas, y luego se apaga mediante la adición de una solución acuosa helada de Na $HSO_3/NaHCO_3/NaOH$, hasta que desaparece el color rojo-castaño de la mezcla. La fase acuosa se ajusta a un pH >10 mediante la adición de hidróxido de sodio sólido con agitación, la fase orgánica se separa, se lava con salmuera, y se filtra. La remoción del solvente (CH_2Cl_2) se logra mediante

destilación a presión atmosférica (<35°C, temperatura de ebullición). Las fracciones que hierven entre 37°C y 110°C se combinan, se recuperan en CH_2Cl_2 (100 mililitros), y se lavan con HCl acuoso 2N. La capa acuosa se vuelve a extraer con CH_2Cl_2 (40 mililitros), los orgánicos combinados se secan (Na_2SO_4), y se filtran. El solvente se retira en un aparato de destilación a presión normal (baño de aceite a 50°C), para obtener el compuesto del título como un líquido amarillo pálido. ^{1}H RMN ($CDCl_3$): δ 1.23 (t, 3H), 1.98 (m, 2H), 3.48-3.57 (m, 4H), 4.12 (t, 2H) ppm. ^{19}F-RMN ($CDCl_3$): δ -60.8 ppm.

c. 3-trifluoro-metoxi-propil-éster del ácido trifluoro-metan-sulfónico.

Siguiendo un procedimiento similar al descrito en *J. Org. Chem.* (2001), 66, 1061-1063, se agrega 1-etoxi-3-trifluoro-metoxi-propano (1.50 gramos, 6.10 milimoles) a una mezcla de anhídrido trifluoro-metan-sulfónico (4.04 mililitros, 23.8 milimoles) y ácido trifluoro-metan-sulfónico (0.15 mililitros, 1.65 milimoles) con agitación. La mezcla se calienta a 60°C durante la noche, se enfría a temperatura ambiente, y se vierte en agua helada. La capa acuosa se extrae con CH_2Cl_2, los orgánicos combinados se secan sobre Na_2SO_4, y se filtran. Los volátiles se retiran mediante destilación a presión normal (temperatura del baño de 65°C), para dar una mezcla de etil-éster del ácido trifluoro-metan-sulfónico y el compuesto del título como un líquido amarillo pálido (utilizado sin

mayor purificación). ^{1}H RMN ($CDCl_3$): δ 2.25 (m, 2H), 4.16 (m, 2H), 4.70 (m, 2H) ppm.

d. 4-bromo-1-metoxi-2-(3trifluoro-metoxi-propoxi)-benceno

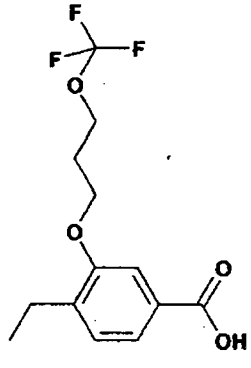
Una mezcla de 5-bromo-2-metoxi-fenol (1.20 gramos, 5.62 milimoles), 3-trifluoro-metoxi-propil-éster del ácido trifluoro-metan-sulfónico (2.52 gramos, 6.74 milimoles; pureza del 74 por ciento), y K_2CO_3 anhidro (1.18 gramos, 8.42 milimoles) en MeCN (8 mililitros), se agita en un matraz sellado a temperatura ambiente durante la noche, y luego se filtra. Los filtrados combinados se concentran, y el producto crudo se pasa por cromatografía sobre gel de sílice (eluyente: tolueno), para dar el compuesto del título como un aceite. TLC, R_f (hexano/AcOEt, 10:1) = 0.63. ^{1}H RMN ($CDCl_3$): β 2.25 (m, 2H), 3.87 (s, 3H), 4.13 (m, 2H), 4.23 (m, 2H), 6.79 (dd, 1H), 7.04 (d, 1H), 7.09 (dd, 1H) ppm. ^{19}F-RMN ($CDCl_3$): δ -60.7 ppm.

e. Ácido 4-metoxi-3-(3-trifluoro-metoxi-propoxi)-benzoico.

A una solución de 4-bromo-1-metoxi-2-(3-trifluoro-metoxi-propoxi)-benceno (1.11 gramos, 3.20 milimoles) en tetrahidrofurano (10 mililitros), enfriada de -60°C a -70°C, se le agrega por goteo una solución 1.6M de N-butil-litio en hexano (2.30 mililitros, 3.69 milimoles). Después de agitar durante 30 minutos, se burbujea una corriente de gas de CO_2 en la solución amarilla durante 10 minutos. La reacción se apaga mediante la

adición de HCl acuoso 2N, y los volátiles se retiran por evaporación. La fase de agua se alcaliza mediante la adición de NaOH 4N, se lava con AcOEt, y luego se acidifica con HCl al 37 por ciento, para formar una suspensión blanca. La extracción con CH_2Cl_2, el secado de los orgánicos sobre Na_2SO_4, y la evaporación, dan el producto del título como un sólido blanco. TLC, R_f (hexano/AcOEt, 1:1) = 0.09. MS: 293.0 $[M-H]^+$; t_R (HPLC, columna Nucleosil C18HD, del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1 mililitro/minuto): 4.00 minutos. ^1H RMN ($CDCl_3$): δ 2.15 (m, 2H), 3.85 (s, 3H), 4.10 (m, 2H), 4.27 (m, 2H), 7.08 (dd, 1H), 7.48 (d, 1H), 7.60 (dd, 1H) ppm. ^{19}F-RMN (DMSO-d_6): δ -58.2 ppm.

Ácido 4-etil-3-(3-trifluoro-metoxi-propoxi)-benzoico



a. Metil-éster del ácido 4-etil-3-(3-trifluoro-metoxi-propoxi)-benzoico.

Una mezcla del metil-éster del ácido 4-etil-3-hidroxi-benzoico (250 miligramos, 1.32 milimoles), 3-trifluoro-metoxi-propil-éster del ácido trifluoro-metan-sulfónico crudo (590

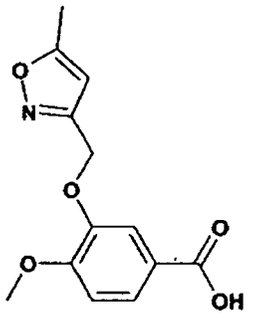
miligramos, 1.58 milimoles; pureza del 74 por ciento), y K_2CO_3 anhidro (276 miligramos, 1.98 milimoles) en MeCN (2.0 mililitros), se agita en un frasco de vidrio sellado durante la noche a temperatura ambiente. El producto crudo obtenido después de la filtración y de la evaporación se purifica mediante cromatografía por evaporación (hexano/AcOEt, 1:1), para dar el compuesto del título como un aceite. TLC, R_f (hexano/AcOEt, 3:1) = 0.38. ^{1}H RMN ($CDCl_3$): δ 1.24 (t, 3H), 2.25 (m, 2H), 2.70 (q, 2H), 3.94 (s, 3H), 4.18 (t, 2H), 4.24 (t, 2H), 7.25 (d, 1H), 7.52 (s, 1H), 7.64 (d, 1H) ppm. ^{19}F-RMN ($CDCl_3$): δ -61.1 ppm.

b. Ácido 4-etil-3-(3-trifluoro-metoxi-propoxi)-benzoico.

El compuesto del título se obtiene a partir de metil-éster del ácido 4-etil-3-(3-trifluoro-metoxi-propoxi)-benzoico (155 miligramos, 0.506 milimoles) mediante hidrólisis en tetrahidrofurano (3 mililitros), en la presencia de NaOH 2N acuoso (0.38 mililitros, 0.76 milimoles) a 60°C durante la noche. Después de enfriar a temperatura ambiente, los volátiles se retiran al vacío, y el residuo se divide entre HCl acuoso 2N y CH_2Cl_2. Los orgánicos combinados se secan (Na_2SO_4), y se evaporan a sequedad, para dar el compuesto del título como un sólido blanco. TLC, R_f (hexano/AcOEt, 1:1) = 0.17. MS: 291.0 $[M-H]^+$; t_R (HPLC, columna Nucleosil C18HD, del 20 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1 mililitro/minuto): 4.99 minutos. ^{1}H RMN (DMSO-d_6): δ 1.15 (t, 3H),

2.18 (m, 2H), 2.64 (q, 2H), 4.13 (t, 2H), 4.29 (t, 2H), 7.28 (d, 1H), 7.45 (s, 1H), 7.51 (d, 1H), 12.65 (s, br, 1H) ppm. ^{19}F-RMN (DMSO-d_6): δ -59.1 ppm.

Ácido 4-metoxi-3-(5-metil-isoxazol-3-ilmetoxi)-benzoico



a. Etil-éster del ácido 4-metoxi-3-(5-metil-isoxazol-3-ilmetoxi)-benzoico.

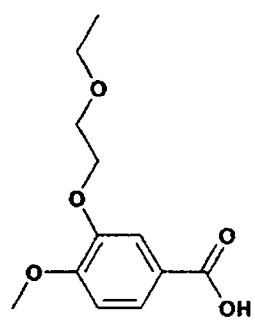
Una mezcla del ácido 3-hidroxi-4-metoxi-benzoico (2.00 gramos, 10.2 milimoles), 3-(cloro-metil)-5-metil-isoxazol (1.61 gramos, 12.2 milimoles; comercialmente disponible en Maybridge, SPB01262DA), K_2CO_3 anhidro (2.11 gramos, 15.3 milimoles), y NaI (0.31 gramos, 2.04 milimoles) en MeCN (35 mililitros), se pone a reflujo durante la noche. Después de enfriar a temperatura ambiente, la mezcla se filtra, el filtrado se diluye con CH_2Cl_2, y los orgánicos se lavan con NaOH 0.5M acuoso, agua, y salmuera. El secado sobre Na_2SO_4 y la evaporación a sequedad proporcionan el compuesto del título crudo como un aceite. MS: 292.0 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18HD, del 5 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1 mililitro/minuto): 4.14 minutos. ^{1}H RMN ($CDCl_3$): δ 1.39 (t, 3H),

2.45 (s, 3H), 3.93 (s, 3H), 4.35 (q, 2H), 5.20 (s, 2H), 6.15 (s, 1H), 6.15 (dd, 1H), 6.90 (d, 1H), 7.70 (dd, 1H) ppm.

b. Ácido 4-metoxi-3-(5-metil-isoxazol-3-ilmetoxi)-benzoico.

El compuesto del título se obtiene mediante la hidrólisis del etil-éster del ácido 4-metoxi-3-(5-metil-isoxazol-3-ilmetoxi)-benzoico (2.90 gramos, 8.96 milimoles), disuelto en EtOH (25 mililitros), en la presencia de NaOH 2N (6.72 mililitros, 13.4 milimoles) a 70°C durante 3 horas. Después de enfriar a temperatura ambiente, los volátiles se retiran al vacío, la fase acuosa se lava con CH_2Cl_2, y luego se acidifica a un pH de 1 mediante la adición de HCl concentrado. El precipitado se filtra y se seca para dar un polvo grisáceo. MS: 264.0 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18HD, del 5 al 100 por ciento de $CH_3CN/H_2O/6$ minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1 mililitro/minuto): 3.98 minutos. ^1H RMN ($CDCl_3$): δ 2.39 (s, 3H), 3.82 (s, 3H), 5.15 (s, 2H), 6.30 (s, 1H), 7.06 (dd, 1H), 7.54 (d, 1H), 7.59 (dd, 1H), 12.7 (s, br, 1H) ppm.

Ácido 3-(2-etoxi-etoxi)-4-metoxi-benzoico



a. Etil-éster del ácido 3-(2-etoxi-etoxi)-4-metoxi-benzoico.

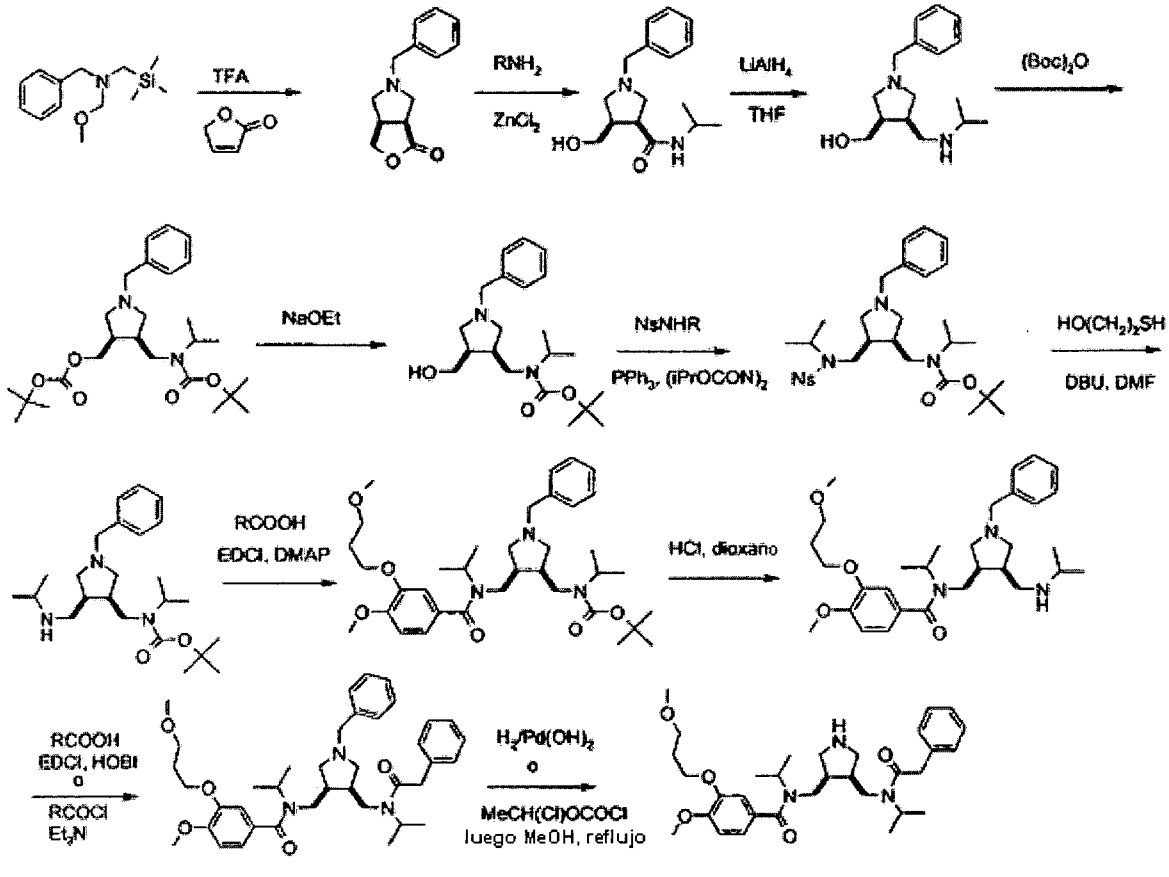
Una mezcla del etil-éster del ácido 3-hidroxi-4-metoxi-benzoico (1.60 gramos, 8.16 milimoles), 2-bromo-etil-etil-éter (1.38 mililitros, 12.2 milimoles) y K_2CO_3 anhidro (1.69 gramos, 12.2 milimoles) en MeCN (35 mililitros), se pone a reflujo durante la noche. Con el objeto de llevar a cabo la reacción, se agregan una alícuota adicional de 2-bromo-etil-etil-éter (1.38 mililitros, 12.2 milimoles), y una cantidad catalítica de NaI, y se continúa el reflujo durante la noche. Después de enfriarse, la mezcla se filtra, y los filtrados se concentran. El residuo se recupera en CH_2Cl_2, la capa orgánica se lava con NaOH 0.5M y agua, se seca (Na_2SO_4), y se concentra. El compuesto del título se obtiene después de la cromatografía por evaporación instantánea (hexano/AcOEt, 8:2) como un aceite incoloro. MS: 269.0 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18HD, del 5 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1 mililitro/minuto): 4.92 minutos. ^1H RMN ($CDCl_3$): δ 1.27 (m, 3H), 1.41 (m, 3H), 3.64 (m, 2H), 3.87 (m, 2H), 3.94 (s, 3H), 4.26 (m, 2H), 4.38 (m, 2H), 9.91 (dd, 1H), 7.63 (d, 1H), 7.72 (dd, 1H) ppm.

b. Ácido 3-(2-etoxi-etoxi)-4-metoxi-benzoico.

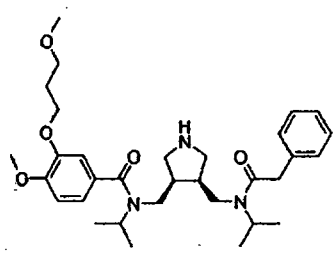
El compuesto del título se obtiene a partir del etil-éster del ácido 3-(2-etoxi-etoxi)-4-metoxi-benzoico (1.41 gramos, 5.26 milimoles), mediante hidrólisis en EtOH (15 mililitros) en la

presencia de NaOH 2N acuoso (3.94 mililitros, 7.88 milimoles) a 50ºC durante la noche, como un polvo blanco. MS: 239.0 $[M-H]^+$; t_R (HPLC, columna Nucleosil C18HD, del 5 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1 mililitro/minuto): 3.78 minutos. ^1H RMN (DMSO-d_6): δ 1.11 (t, 3H), 3.48 (q, 2H), 3.68 (m, 2H), 3.80 (s, 3H), 4.08 (m, 2H), 7.03 (dd, 1H), 7.43 (d, 1H), 7.55 (dd, 1H), 12.6 (s, br, 1H) ppm.

Esquema de reacción 7



Ejemplo 361: N-isopropil-N-{(3R*,4S*)-4-[(isopropil-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-4-metoxi-3-(3-metoxi-propoxi)-benzamida



Una solución de N-{(3R*,4S*)-4-[(isopropil-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida (0.15 gramos, 0.24 milimoles) y cloroformato de 1-cloro-etilo (0.10 mililitros, 0.97 milimoles) en $ClCH_2CH_2Cl$, se pone a reflujo durante 2 horas bajo una atmósfera de nitrógeno, y luego se agrega MeOH (10 mililitros) a temperatura ambiente. La mezcla se calienta durante 2 horas a 80°C, y se concentra para dar el producto del título. Para la purificación, se prepara el compuesto protegido por N-Boc, terbutil-éster del ácido (3S*,4R*)-3-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-4-[(isopropil-fenil-acetil-amino)-metil]-pirrolidin-1-carboxílico, de una manera análoga a la descrita para el compuesto del título D en el Ejemplo 361, Esquema de reacción 7. El producto crudo se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente: ciclohexano/AcOEt, 50/50), para dar el producto. MS (LC-MS): 654.4 $[M+H]^+$; t_R (HPLC, columna C18, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/2.5 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-

acético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.92 minutos.

El compuesto del título puro se prepara de una manera análoga a la descrita para el compuesto del título bajo I en el Ejemplo 361, Esquema de reacción 7. MS (LC-MS): 554.4 $[M+H]^+$; t_R (HPLC, columna C18, del 10 al 100 por ciento de $CH_3CN/H_2O/5$ minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.23 minutos.

A. (3aR*,6aS*)-5-bencil-hexahidro-furo-[3,4-c]-pirrol-1-ona.

A una mezcla de γ-crotonolactona (0.99 mililitros, 13.5 milimoles) y N-(metoxi-metil)-N-(trimetil-silil-metil)-bencil-amina (5.0 gramos, 20.2 milimoles) en CH_2Cl_2 (50 mililitros), se le agrega por goteo ácido trifluoro-acético (0.10 mililitros, 1.30 milimoles) a 0°C. La mezcla de reacción se agita durante la noche a temperatura ambiente, y se apaga con una solución acuosa saturada de $NaHCO_3$ (30 mililitros). Se agrega CH_2Cl_2, las capas se separan, y la acuosa se retro-extrae dos veces con CH_2Cl_2. Los extractos orgánicos combinados se secan sobre $MgSO_4$, se filtran, y se concentran. El material crudo se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente: AcOEt/hexano, 10:90 a 20:80), para dar el producto del título. TLC, R_f (AcOEt/hexano, 3:7) = 0.73. MS (LC-MS): 218.1 $[M+H]^+$; t_R (HPLC, columna C18, del 10 al 100 por ciento de $CH_3CN/H_2O/5$ minutos, 100 por ciento de CH_3CN/2.5 minutos,

CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 2.95 minutos.

B. Isopropil-amida del ácido (3S*,4R*)-1-bencil-4-hidroxi-metil-pirrolidin-3-carboxílico.

Una suspensión de (3aR*,6aS*)-5-bencil-hexahidro-furo-[3,4-c]-pirrol-1-ona (1.50 gramos, 6.90 milimoles) y $ZnCl_2$ (0.94 gramos, 6.90 milimoles) en $iPrNH_2$ (20 mililitros), se pone a reflujo durante la noche bajo una atmósfera de nitrógeno. El material crudo se filtra sobre un cojín de Celite, y se concentra. El material crudo se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente: CH_2Cl_2/MeOH/NH_4OH, 70:25:5), para dar el producto del título. TLC, R_f (CH_2Cl_2/MeOH, 95:5) = 0.38. MS (LC-MS): 277.2 $[M+H]^+$.

C. [(3R*,4R*)-1-bencil-4-(isopropil-amino-metil)-pirrolidin-3-il]-metanol.

A una solución helada de $LiAlH_4$ (0.56 gramos, 14.76 milimoles) en tetrahidrofurano (25 mililitros) se le agrega por goteo una solución de isopropil-amida del ácido (3S*,4R*)-1-bencil-4-hidroxi-metil-pirrolidin-3-carboxílico (1.02 gramos, 3.69 milimoles) en tetrahidrofurano (5 mililitros). La mezcla de reacción se pone a reflujo durante la noche, y se apaga con $Na_2SO_4 \cdot 10H_2O$ (4 gramos) a 0°C. Se agrega éter, la mezcla se agita durante 2 horas a temperatura ambiente. El material crudo se filtra sobre un cojín de

Celite, y se concentra para dar el compuesto del título, el cual se utiliza sin mayor purificación en el siguiente paso. TLC, R_f (CH_2Cl_2/MeOH, 95:5) = 0.28. MS (LC-MS): 263.2 $[M+H]^+$; t_R (HPLC, columna C18, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/2.5 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 2.94 minutos.

D. Terbutil-éster de (3R*,4S*)-1-bencil-4-[(terbutoxi-carbonil-isopropil-amino)-metil]-pirrolidin-3-ilmetil-éster del ácido carbónico.

Una suspensión de [(3R*,4R*)-1-bencil-4-(isopropil-amino-metil)-pirrolidin-3-il]-metanol (1.13 gramos, 4.31 milimoles), $NaHCO_3$ (1.45 gramos, 17.24 milimoles), y Boc_2O (1.88 gramos, 8.62 milimoles) en MeOH (50 mililitros) se agita durante la noche a temperatura ambiente. La mezcla se calienta durante 1 hora a 65°C, y luego se concentra hasta unos cuantos mililitros de solvente mediante evaporación giratoria. Se agregan agua y CH_2Cl_2, las capas se separan, y la acuosa se extrae dos veces con CH_2Cl_2. Los extractos orgánicos combinados se secan ($MgSO_4$), y se concentran, para dar el compuesto del título, el cual se utiliza sin mayor purificación en el siguiente paso. TLC, R_f (AcOEt) = 0.81. MS (LC-MS): 463.3 $[M+H]^+$; t_R (HPLC, columna C18, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/2.5 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-

acético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 6.08 minutos.

E. Terbutil-éster del ácido {(3S*,4R*)-1-bencil-4-hidroxi-metil-pirrolidin-3-ilmetil)-isopropil-carbámico.

Una mezcla del terbutil-éster de (3R*,4S*)-1-bencil-4-[(terbutoxi-carbonil-isopropil-amino)-metil]-pirrolidin-3-ilmetil-éster del ácido carbónico (2.02 gramos, 4.31 milimoles) y NaOEt (0.59 gramos, 8.62 milimoles) en EtOH (35 mililitros), se agita durante 2 horas a temperatura ambiente. El solvente se concentra, y el residuo se diluye con CH_2Cl_2 y H_2O. Las capas se separan, y el extracto orgánico se lava sucesivamente con H_2O y salmuera. Las capas orgánicas combinadas se secan con $MgSO_4$, se filtran, y se concentran. El material crudo se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente: CH_2Cl_2/MeOH, 95:5), para dar el producto del título. TLC, R_f (AcOEt) = 0.23. MS (LC-MS): 363.3 $[M+H]^+$; t_R (HPLC, columna C18, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/2.5 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.06 minutos.

F. Terbutil-éster del ácido ((3S*,4R*)-1-bencil-4-{[isopropil-(2-nitro-bencen-sulfonil)-amino]-metil}-pirrolidin-3-ilmetil)-isopropil-carbámico.

A una solución del terbutil-éster del ácido ((3S*,4R*)-1-

bencil-4-hidroxi-metil-pirrolidin-3-ilmetil)-isopropil-carbámico (0.60 gramos, 1.66 milimoles), N-isopropil-2-nitro-bencen-sulfonamida (0.49 gramos, 1.99 milimoles), y PPh_3 (0.52 gramos, 1.99 milimoles) en tolueno (15 mililitros), se le agrega por goteo azodicarboxilato de di-isopropilo (0.39 mililitros, 1.99 milimoles) a 0°C bajo una atmósfera de nitrógeno. La solución se agita durante 1 hora a temperatura ambiente, y luego se calienta a 65°C durante 1 hora. La mezcla de reacción se concentra. El material crudo se utiliza purificado mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente: ciclohexano/AcOEt, 3:7), para dar el producto crudo. Al producto sólido, se le agrega una mezcla de Et_2/hexano (1:1), y la solución resultante se filtra. El sólido se lava con una solución de Et_2/hexano (1:1), y luego el filtrado combinado se concentra para dar el producto del título. TLC, R_f (AcOEt) = 0.61. MS (LC-MS): 589.3 $[M+H]^+$; t_R (HPLC, columna C18, del 10 al 100 por ciento de CH_3CN/H_2O/6 minutos, 100 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 6.39 minutos.

G. Terbutil-éster del ácido [(3S*,4S*)-1-bencil-4-(isopropil-amino-metil)-pirrolidin-3-ilmetil]-isopropil-carbámico.

Una solución del terbutil-éster del ácido ((3S*,4R*)-1-bencil-4-{[isopropil-(2-nitro-bencen-sulfonil)-amino]-metil}-pirrolidin-3-ilmetil)-isopropil-carbámico (8.9 gramos, 23.02 milimoles), 2-

mercapto-etanol (0.81 mililitros, 11.60 milimoles), y DBU (0.79 mililitros, 5.27 milimoles) en CH_3CN (10 mililitros), se agita durante 2 horas a temperatura ambiente. La mezcla se concentra, y luego se diluye con Et_2O y H_2O. La capa orgánica se separa, y la fase acuosa se extrae tres veces con Et_2O. Los extractos orgánicos combinados se secan ($MgSO_4$), y el solvente se concentra para dar el compuesto del título, el cual se utiliza sin mayor purificación en el siguiente paso. TLC, R_f (AcOEt) = 0.61. MS (LC-MS): 404.3 $[M+H]^+$; t_R (HPLC, columna C18, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/2.5 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 4.45 minutos.

H. Terbutil-éster del ácido [(3S*,4R*)-1-bencil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-isopropil-carbámico.

A una solución del terbutil-éster del ácido [(3S*,4S*)-1-bencil-4-(isopropil-amino-metil)-pirrolidin-3-ilmetil]-isopropil-carbámico (0.32 gramos, 0.55 milimoles), ácido 4-metoxi-3-(3-metoxi-propoxi)-benzoico (0.23 gramos, 0.96 milimoles), DMAP (0.12 gramos, 0.96 milimoles), y trietil-amina (0.56 mililitros, 0.96 milimoles) en dimetil-formamida (10 mililitros), se le agrega EDCI-HCl (0.19 gramos, 0.96 milimoles) a 0°C. La mezcla de reacción se agita durante la noche a temperatura ambiente. Se agregan agua y EtO_2, las capas se separan, y la acuosa se extrae dos veces con Et_2O. Los extractos orgánicos combinados se secan ($MgSO_4$), y el

solvente se retira al vacío. El producto crudo se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente: CH_2Cl_2/MeOH, 90:10), para dar el producto del título. TLC, R_f (CH_2Cl_2/MeOH, 9:1) = 0.72. MS (LC-MS): 626.4 $[M+H]^+$; t_R (HPLC, columna C18, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/2.5 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 6.28 minutos.

I.N-[(3R*,4R*)-1-bencil-4-(isopropil-amino-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida.

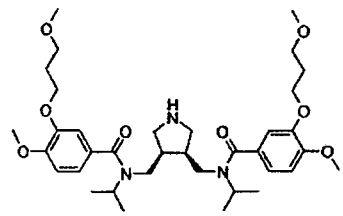
A una solución de terbutil-éster del ácido [(3S*,4R*)-1-bencil-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-isopropil-carbámico (0.41 gramos, 0.66 milimoles), se le agrega una solución en dioxano de HCl 4N (10 mililitros). La mezcla de reacción se agita durante 2 horas a temperatura ambiente. El solvente se concentra, y se agregan agua (20 mililitros), una solución acuosa de NaOH 4N (5 mililitros) y Et_2O (25 mililitros). Las capas se separan, y la acuosa se extrae dos veces con Et_2O. Los extractos orgánicos combinados se secan ($MgSO_4$), y el solvente se retira al vacío, para dar el compuesto del título, el cual se utiliza sin mayor purificación en el siguiente paso. MS (LC-MS): 526.4 $[M+H]^+$; t_R (HPLC, columna C18, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/2.53 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 4.78 minutos.

J. N-{(3R*,4S*)-1-bencil-4-[(isopropil-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida.

A una solución de N-[(3R*,4R*)-1-bencil-4-(isopropil-amino-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida (0.19 gramos, 0.36 milimoles), trietil-amina (0.15 mililitros, 1.09 milimoles), y DMAP (0.013 gramos, 0.11 milimoles) en CH_2Cl_2, se le agrega por goteo cloruro de fenil-acetilo (0.058 mililitros, 0.44 milimoles) a 0°C bajo una atmósfera de nitrógeno. La solución se agita durante la noche a temperatura ambiente. La mezcla se agrega a una solución acuosa de NaOH 0.1N (50 mililitros) y CH_2Cl_2 (50 mililitros). La capa orgánica se separa, y la fase acuosa se extrae dos veces con CH_2Cl_2, se seca sobre $MgSO_4$, se filtra, y se concentra al vacío. El producto crudo se purifica mediante cromatografía por evaporación instantánea sobre gel de sílice (eluyente: CH_2Cl_2/MeOH, 90:10), para dar el producto del título. TLC, R_f (CH_2Cl_2/MeOH, 9:1) = 0.23. MS (LC-MS): $[M+H]^+$; t_R (HPLC, columna C18, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/2.5 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.95 minutos.

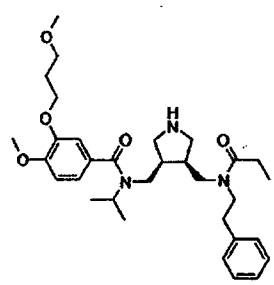
Los siguientes Ejemplos se preparan de acuerdo con los procedimientos descritos anteriormente para el Ejemplo 361:

Ejemplo 362: N-isopropil-N-{(3R*,4S*)-4-[(isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzoil-amino)-metil]-pirrolidin-3-ilmetil)-4-metoxi-3-(3-metoxi-propoxi)-benzamida



El compuesto del título se prepara de una manera análoga a la descrita en el Ejemplo 361, mediante el acoplamiento de N-[(3R*,4R*)-1-bencil-4-(isopropil-amino-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida y ácido 3-(3-metoxi-propoxi)-4-metoxi-benzoico en el paso J. MS (LC-MS): 658.3 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/2.5 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.20 minutos.

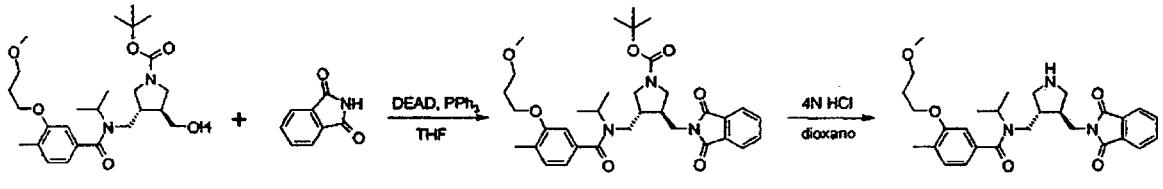
Ejemplo 363: N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-N-{(3R,4S)-4-[(fenetil-propionil-amino)-metil]-pirrolidin-3-ilmetil}-benzamida



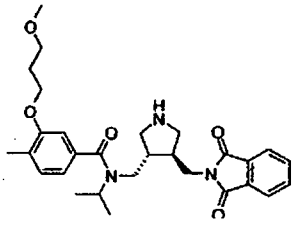
El compuesto del título se prepara de una manera análoga a

la descrita en el Ejemplo 361, utilizando el terbutil-éster del ácido ((3S*,4R*)-1-bencil-4-hidroxi-metil-pirrolidin-3-ilmetil)-isopropil-carbámico y 2-nitro-N-fenetil-bencen-sulfonamida en el paso F, y luego cloruro de propionilo como el agente de acilación en el paso H, y ácido 3-(3-metoxi-propoxi)-4-metoxi-benzoico como agente de acilación en el paso J. MS (LC-MS): 554.4 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.26 minutos.

Esquema de reacción 8



Ejemplo 364: N-[(3S,4S)-4-(1,3-dioxo-1,3-dihidro-isoindol-2-ilmetil)-pirrolidin-3-ilmetil]-N-isopropil-3-(3-metoxi-propoxi)-4-metil-benzamida



El terbutil-éster del ácido (3R,4R)-3-(1,3-dioxo-1,3-dihidro-isoindol-2-ilmetil)-4-({isopropil-[3-(3-metoxi-propoxi)-4-metil-

benzoil]-amino}-metil)-pirrolidin-1-carboxílico (180 miligramos, 0.30 milimoles) se disuelve en HCl 4N en dioxano (5 mililitros), y se agita a temperatura ambiente durante 30 minutos. La liofilización proporciona la sal de clorhidrato correspondiente. MS (LC-MS): 508.1 $[M+H]^+$; t_R (HPLC, columna Waters Symmetry C18, del 20 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/2 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 0.6 mililitros/minuto): 2.58 minutos.

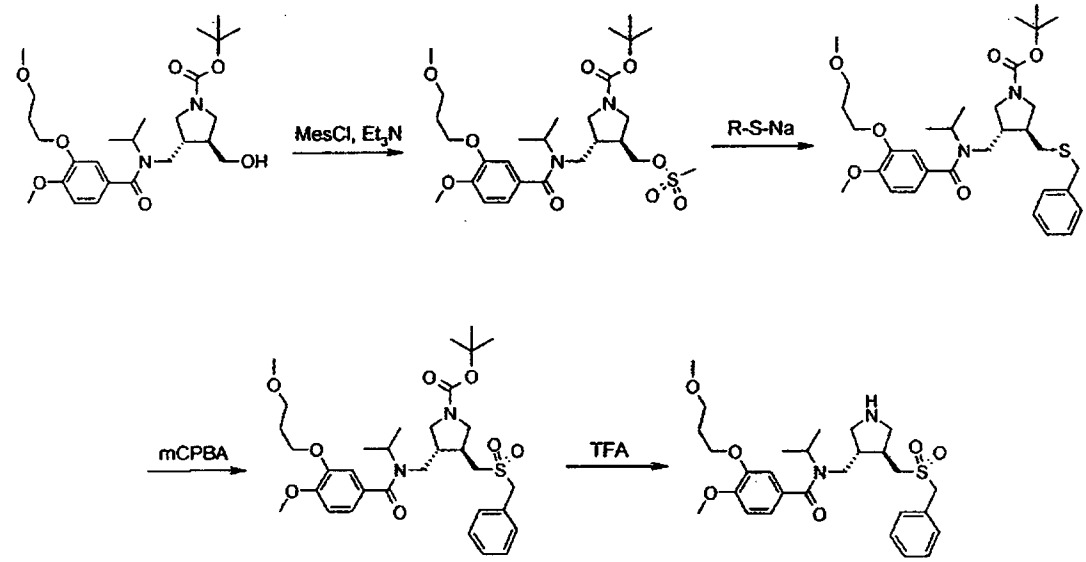
El material de inicio se prepara como sigue:

Terbutil-éster del ácido (3R,4R)-3-(1,3-dioxo-1,3-dihidro-isoindol-2-ilmetil)-4-({isopropil-[3-(3-metoxi-propoxi)-4-metil-benzoil]-amino}-metil)-pirrolidin-1-carboxílico.

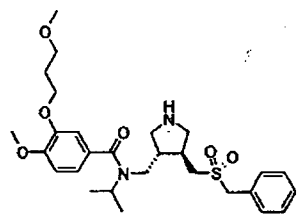
Se agrega lentamente DEAD a una solución de terbutil-éster del ácido (3S,4R)-3-hidroxi-metil-4-({isopropil-[3-(3-metoxi-propoxi)-4-metil-benzoil]-amino}-metil)-pirrolidin-1-carboxílico (210 miligramos, 0.44 milimoles), ftalimida (0.7 miligramos, 0.66 milimoles), y PPh_3 (173 miligramos, 0.66 milimoles) en tetrahidrofurano (5 mililitros) a temperatura ambiente. La solución amarilla resultante se agita durante otras 2 horas antes de agregar H_2O, y la mezcla se extrae con acetato de etilo. El secado (Na_2SO_4) de los extractos, la filtración, y la evaporación del solvente, proporcionan el producto crudo, el cual se purifica mediante HPLC de preparación (Waters C_{18} ODB, eluyente: CH_3CN/H_2O al 5 por ciento/2 minutos, CH_3CN/H_2O al 5-100 por

ciento/10 minutos, 100 por ciento de CH_3CN/2.5 minutos, flujo: 20 mililitros/minuto), para dar el producto deseado. MS (LC-MS): 630.2 $[M+H]^+$; t_R (HPLC, columna Waters Symmetry C18, del 20 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento CH_3CN/H_2O, 2 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 0.6 mililitros/minuto): 4.40 minutos.

Esquema de reacción 9:

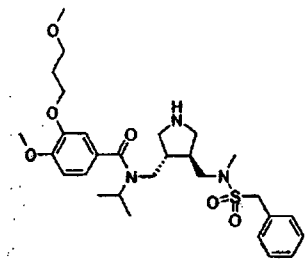


Ejemplo 365: N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-N-((3S*,4S*)-4-fenil-metan-sulfonil-metil-pirrolidin-3-ilmetil)-benzamida



El compuesto del título se prepara como se muestra en el Esquema de reacción 9.

Ejemplo 366: N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-N-{(3S*,4S*)-4-[(metil-fenil-metan-sulfonil-amino)-metil]-pirrolidin-3-ilmetil}-benzamida



A una solución del terbutil-éster del ácido (3R*,4S*)-isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-4-[(metil-fenil-metan-sulfonil-amino)-metil]-pirrolidin-1-carboxílico (49 miligramos, 0.074 milimoles) en 2 mililitros de CH_2Cl_2, se le agrega ácido trifluoro-acético (86 microlitros, 1.11 milimoles). La mezcla se agita durante 4 horas a temperatura ambiente, y luego se vierte en una solución saturada de $NaHCO_3$. Las capas se separan, y la acuosa se retro-extrae dos veces con CH_2Cl_2. Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran, y se concentran. El material crudo se purifica mediante cromatografía por evaporación instantánea sobre una columna Isolute SPE Flash NH_2 (eluyente: CH_2Cl_2/MeOH, 100:0 a 95:5), para dar el producto del título. TLC, R_f (CH_2Cl_2/MeOH, 9:1) = 0.2. MS (LC-MS): 563.0 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18, del 10 al 100 por ciento de CH_3CN/5 minutos, 100 por ciento CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 4.55 minutos.

A una solución de la base libre en dioxano (2 mililitros), se

le agrega HCl 4N en dioxano (0.074 milimoles, 19 microlitros), y la solución resultante se liofiliza para proporcionar la sal de clorhidrato correspondiente como un polvo blanco.

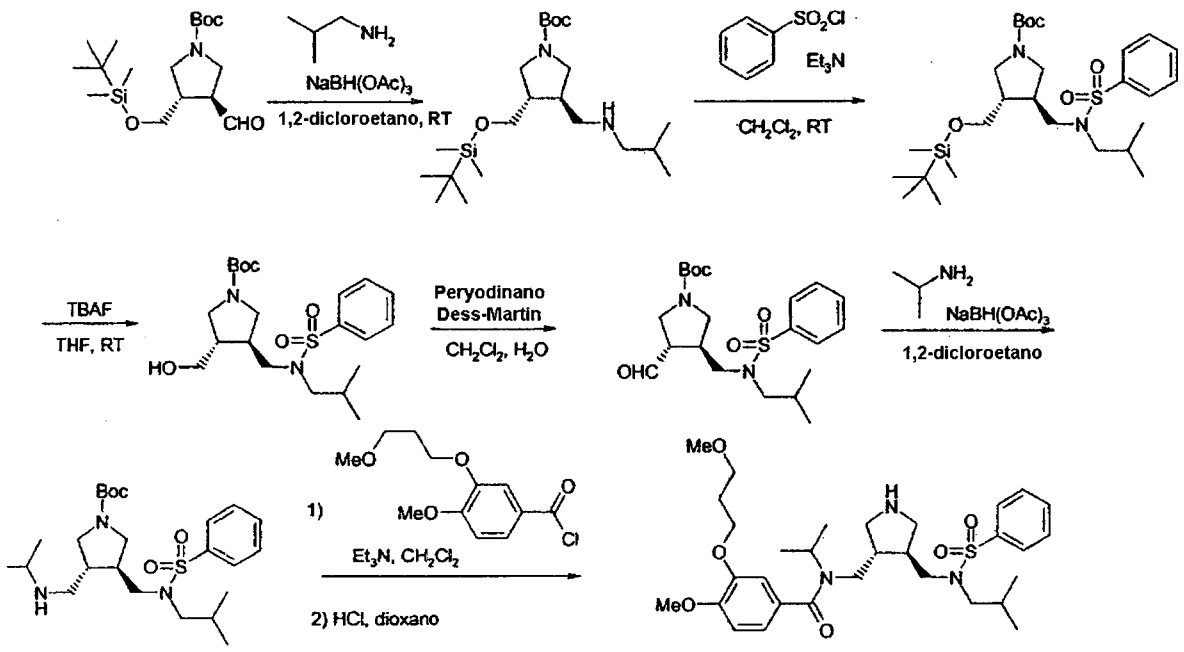
El material de inicio se prepara como sigue:

Terbutil-éster del ácido (3R*,4S*)-3-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-4-[(metil-fenil-metan-sulfonil-amino)-metil]-pirrolidin-1-carboxílico.

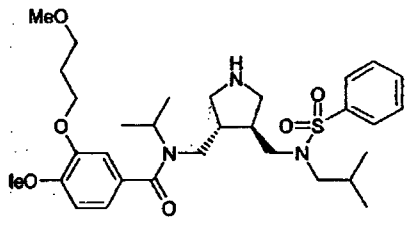
A una solución del terbutil-éster del ácido (3R*,4R*)-3-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-4-metil-amino-metil-pirrolidin-1-carboxílico (89 miligramos, 0.175 milimoles) en CH_2Cl_2 (3 mililitros), se le agregan cloruro de alfa-toluensulfonilo (40 miligramos, 0.21 milimoles) y trietil-amina (30 microlitros, 0.21 milimoles) bajo una atmósfera de N_2. La mezcla se agita durante la noche a temperatura ambiente, se diluye con CH_2Cl_2, y se vierte en una solución acuosa saturada de $NaHCO_3$. La capa orgánica se separa, y la acuosa se extrae dos veces con CH_2Cl_2. Los extractos orgánicos combinados se secan sobre Na_2SO_4, se filtran, y se concentran. El producto crudo se purifica mediante HPLC de preparación (C18-ODB-AQ, 5 micras, 20 x 50 milímetros, YMC, eluyente: CH_3CN/H_2O + HCOOH al 0.1 por ciento, flujo: 20 mililitros/minuto). Las fracciones de la HPLC se recolectan, y la solución resultante se liofiliza para proporcionar el producto del título. TLC, R_f (CH_2Cl_2/MeOH, 95:5) = 0.3. t_R (HPLC, columna Nucleosil C18, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O

conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 5.81 minutos.

Esquema de reacción 10



Ejemplo 367: N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-N-{(3S*,4S*)-4-[(isobutil-fenil-sulfonil-amino)-metil]-pirrolidin-3-ilmetil}-benzamida



Se agrega HCl 4N/dioxano (4 mililitros) a una solución del terbutil-éster del ácido (3R*,4R*)-3-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-4-[(isobutil-fenil-sulfonil-

amino)-metil]-pirrolidin-1-carboxílico (0.804 gramos, 1.17 milimoles) en dioxano (5 mililitros). Después de 3 horas, la solución se liofiliza para dar el compuesto del título como un polvo incoloro. MS (LC-MS): 590.3 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 4.91 minutos.

El material de inicio se prepara como sigue:

A. Terbutil-éster del ácido (3S*,4R*)-3-(terbutil-dimetil-silaniloxi-metil)-4-(isobutil-amino-metil)-pirrolidin-1-carboxílico.

El compuesto del título se prepara como se describe anteriormente en el Ejemplo 9/paso F (Esquema de reacción 5), a partir del terbutil-éster del ácido (3S*,4S*)-3-(terbutil-dimetil-silaniloxi-metil)-4-formil-pirrolidin-1-carboxílico e isobutil-amina. MS (LC-MS): 401.1 $[M+H]^+$; t_R (HPLC, columna Waters Symmetry C18, del 20 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/H_2O, 2 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 0.6 mililitros/minuto): 3.70 minutos.

B. N-[(3S*-4S*)-4-(terbutil-dimetil-silaniloxi-metil)-pirrolidin-3-ilmetil]-N-isobutil-bencen-sulfonamida.

El compuesto del título se prepara como se describe anteriormente en el Ejemplo 366/paso A, a partir del terbutil-éster

del ácido (3S*,4R*)-3-(terbutil-dimetil-silaniloxi-metil)-4-(isobutil-amino-metil)-pirrolidin-1-carboxílico y cloruro de fenil-sulfonilo. TLC, R_f (CH_2Cl_2/MeOH, 98:2) = 0.42; t_R (HPLC, columna Waters Symmetry C18, del 20 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/H_2O, 2 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 0.6 mililitros/minuto): 5.58 minutos.

C. N-((3S*,4S*)-4-hidroxi-metil-pirrolidin-3-ilmetil)-N-isobutil-bencen-sulfonamida.

El compuesto del título se prepara como se describe anteriormente para el Ejemplo 9/paso H (Esquema de reacción 5), a partir de la N-[(3S*,4S*)-4-(terbutil-dimetil-silaniloxi-metil)-pirrolidin-3-ilmetil]-N-isobutil-bencen-sulfonamida. MS (LC-MS): 327.1 $[M\text{-}Boc+H]^+$; t_R (HPLC, columna Waters Symmetry C18, del 20 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/H_2O, 2 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 0.6 mililitros/minuto): 4.17 minutos.

D. N-((3S*,4S*)-4-formil-pirrolidin-3-ilmetil)-N-isobutil-bencen-sulfonamida.

El compuesto del título se prepara como se describe anteriormente para el Ejemplo 9/paso E (Esquema de reacción 5), a partir de N-((3S*,4S*)-4-hidroximetil-pirrolidin-3-ilmetil)-N-isobutil-bencen-sulfonamida. MS (LC-MS): 325.0 $[M\text{-}Boc+H]^+$; t_R

(HPLC, columna Waters Symmetry C18, del 20 al 95 por ciento de CH_3CN/H_2O/3.5 minutos, 95 por ciento de CH_3CN/H_2O, 2 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 0.6 mililitros/ minuto): 4.24 minutos.

E. Terbutil-éster del ácido (3S*,4R*)-3-[(bencen-sulfonil-isobutil-amino)-metil]-4-(isopropil-amino-metil)-pirrolidin-1-carboxílico.

El compuesto del título se prepara como se describe anteriormente para el Ejemplo 9/paso F (Esquema de reacción 5), a partir de N-((3S*,4S*)-4-formil-pirrolidin-3-ilmetil)-N-isobutil-bencen-sulfonamida e isopropil-amina. MS (LC-MS): 468.1 $[M+H]^+$; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 4.94 minutos.

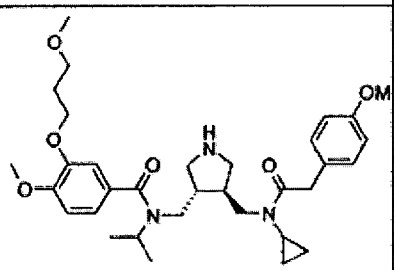
F. Terbutil-éster del ácido (3R*,4R*)-3-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-4-[(isobutil-fenil-sulfonil-amino)-metil]-pirrolidin-1-carboxílico.

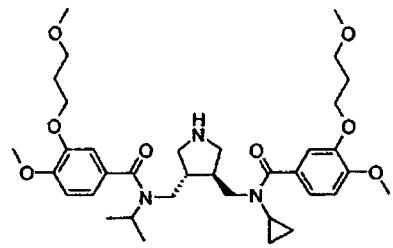
Se agregan trietil-amina (0.48 mililitros, 3.43 milimoles), seguida por cloruro del ácido 3-(3-metoxi-propoxi)-4-metoxi-benzoico (621 miligramos, 2.4 milimoles) (preparado a partir de ácido 3-(3-metoxi-propoxi)-4-metoxi-benzoico y $SOCl_2$ en CH_2Cl_2), a una solución de terbutil-éster del ácido (3S*,4R*)-3-[(bencen-

sulfonil-isobutil-amino)-metil]-4-(isopropil-amino-metil)-pirrolidin-1-carboxílico (1.07 gramos, 2.3 milimoles) en CH_2Cl_2 (30 mililitros), y se agitan a temperatura ambiente durante 16 horas. Para el procesamiento, se agrega una solución saturada de $NaHCO_3$, y la mezcla se extrae con acetato de etilo. Los extractos orgánicos combinados se secan (Na_2SO_4), se filtran, y el solvente se evapora. La purificación del producto crudo mediante cromatografía por evaporación instantánea sobre gel de sílice (gradiente de eluyente: ciclohexano/AcOEt, 1:1 a 3:7) produce el compuesto del título. TLC, R_f (ciclohexano/AcOEt, 3:7) = 0.40; t_R (HPLC, columna Nucleosil C18 de Macherey-Nagel, del 10 al 100 por ciento de CH_3CN/H_2O/5 minutos, 100 por ciento de CH_3CN/3 minutos, CH_3CN y H_2O conteniendo ácido trifluoro-acético al 0.1 por ciento, flujo: 1.5 mililitros/minuto): 6.10 minutos.

Los siguientes Ejemplos se preparan de acuerdo con los procedimientos descritos anteriormente en los Ejemplos 8, 9, 10, 11, 12, y 13:

Tabla 19:

Ejemplo	Configuración	Estructura	$[M+H]^+$	t_R (HPLC)
368	(3S*, 4S*)		582.4	4.51

369	(3S,4S)		656.4	4.37

Condiciones de RP-HPLC: columna: Nucleosil C18-HD (4 x 70 milímetros, 3 micras); solvente A: H_2O/ácido trifluoro-acético al 0.1 por ciento, solvente B: MeCN/ácido trifluoro-acético al 0.1 por ciento; gradiente: del 5 al 100 por ciento del solvente B durante 6 minutos, luego el 100 por ciento del solvente B durante 1.5 minutos, luego del 100 al 5 por ciento del solvente B durante 0.5 minutos; flujo: 1.0 mililitros/minuto.

Ejemplo 370: Cápsulas Blandas

Se preparan 5,000 cápsulas de gelatina blanda, cada una comprendiendo, como ingrediente activo, 0.05 gramos de cualquiera de los compuestos de la Fórmula I mencionados en cualquiera de los Ejemplos anteriores, como sigue:

1. Composición

Ingrediente activo	250 gramos
Lauroglicol	2 litros.

Proceso de preparación: El ingrediente activo pulverizado se suspende en Lauroglykol® (laurato de propilenglicol, Gattefossé S.A., Saint Priest, Francia), y se muele en un pulverizador húmedo para producir un tamaño de partículas de aproximadamente 1 a 3

micras. Entonces se introducen porciones de 0.419 gramos de la mezcla en cápsulas de gelatina blanda, utilizando una máquina llenadora de cápsulas.

Ejemplo 371: Tabletas que comprenden a los compuestos de la Fórmula I.

Se preparan tabletas que comprenden, como ingrediente activo, 100 miligramos de cualquiera de los compuestos de la Fórmula I de cualquiera de los Ejemplos anteriores, con la siguiente composición, siguiendo los procedimientos convencionales:

Composición

Ingrediente activo	100 mg
Lactosa cristalina	240 mg
Avicel	80 mg
PVPPXL	20 mg
Aerosil	2 mg
Estearato de magnesio	5 mg
	447 mg

Fabricación: El ingrediente activo se mezcla con los materiales de vehículo, y se comprime por medio de una máquina formadora de tabletas (Korsch EKO, diámetro de troquel de 10

milímetros).

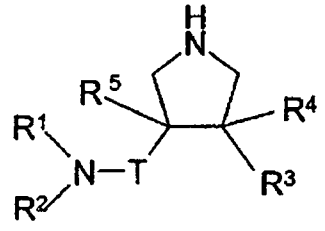
Avicel® es celulosa microcristalina (FMC, Filadelfia, EUA). PVPPXL es polivinil-polipirrolidona, reticulada (BASF, Alemania). Aerosil® es dióxido de silicio (Degussa, Alemania).

Ejemplo 372: Actividad inhibidora de renina de los compuestos de los Ejemplos 1 a 369:

Utilizando los sistemas de prueba mencionados anteriormente, se pueden encontrar los valores IC_{50} para los compuestos de los Ejemplos 1 a 369 anteriores, en el intervalo de 1 nM a 20 µM.

REIVINDICACIONES

1. El uso de un compuesto de la Fórmula I:



(I)

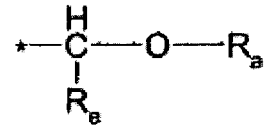
en donde:

R^1 es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, alquenilo insustituido o sustituido, alquinilo insustituido o sustituido, o acilo;

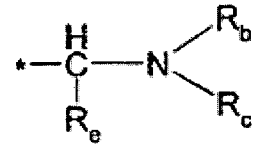
R^2 es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, alquenilo insustituido o sustituido, alquinilo insustituido o sustituido, o acilo;

R^3 es una fracción seleccionada a partir del grupo de fracciones de las fórmulas:

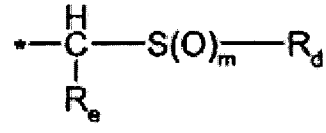
(a)



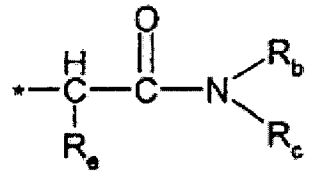
(b)



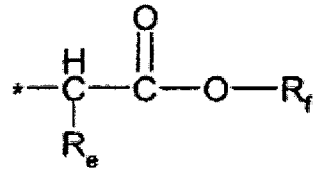
(c)



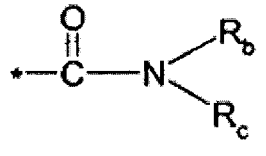
(d)



(e)

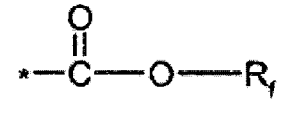


(f)



y

(g)



en donde, en cualquiera de las fracciones de las fórmulas dadas anteriormente bajo (a), (b), (c), (d), (e), (f), y (g), el

asterisco (*) muestra en enlace que enlaza a la fracción R^3 respectiva con el resto de la molécula en la Fórmula I,

R_a es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, acilo, o hidrógeno;

R_b y R_c se seleccionan independientemente a partir de las fracciones dadas en R_a, con la condición de que de preferencia no más de uno de R_b y R_c sea acilo; o R_b y R_c pueden formar juntos un anillo de 3 a 7 miembros que contenga nitrógeno, el cual puede estar insustituido o sustituido;

R_d es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, o acilo, o puede tener uno de estos significados, o puede ser $-N(R_b(R_c)$ si **m** es 1 ó de preferencia 2;

R_e es hidrógeno, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o

sustituido, o alquilo de 1 a 7 átomos de carbono sustituido o de preferencia insustituido; y

R_f es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido;

m es 0, 1, ó 2;

cada uno de R^4 y R^5 se selecciona, independiente-mente uno del otro, a partir de hidrógeno, alquilo insustituido o sustituido, hidroxi, o hidroxi esterificado o eterificado;

y T es metileno, metileno mono-sustituido por alquilo, o es carbonilo o tio-carbonilo;

o una sal farmacéuticamente aceptable del mismo,

en la preparación de una formulación farmacéutica para el tratamiento de una enfermedad que dependa de la actividad de la renina.

2. El uso de acuerdo con la reivindicación 1, de un compuesto de la Fórmula I, en donde:

R^1 es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o

sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, alquenilo insustituido o sustituido, alquinilo sustituido o insustituido, o acilo;

R^2 es arilo mono- o bi-cíclico-alquilo insustituido o sustituido;

R^3 es una fracción seleccionada a partir del grupo de fracciones de las fórmulas (a), (b), (c), (d), (e), (f), ó (g) dadas en la primera descripción de un compuesto de la Fórmula I en esta divulgación;

en donde, en cualquiera de las fracciones de las fórmulas de fracciones, el asterisco (*) muestra el enlace que enlaza a la fracción R^3 respectiva con el resto de la molécula en la Fórmula I,

R_a es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, acilo, o hidrógeno;

R_b y R_c se seleccionan independientemente a partir de las fracciones dadas en R_a, con la condición de que, de preferencia, no más de uno de R_b y R_c sea acilo;

R_d es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico

insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, o (de preferencia si **m** es 0) acilo, o puede tener uno de estos significados, o puede ser $-N(R_b(R_c)$ si **m** es 1 ó de preferencia 2;

R_e es arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, o alquilo de 1 a 7 átomos de carbono sustituido o de preferencia insustituido, o hidrógeno; y

R_f es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido;

m es 0, 1, ó 2;

cada uno de R^4 y R^5 se selecciona, independiente-mente uno del otro, a partir de hidrógeno, alquilo insustituido o sustituido, hidroxi, o hidroxi esterificado o eterificado, de preferencia hidrógeno;

y T es metileno ($-CH_2-$), metileno mono-sustituido por

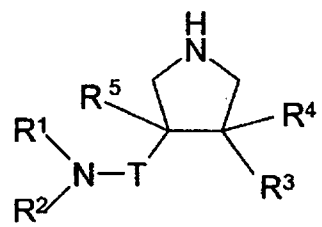
alquilo (-[C(H)(alquilo)]-), carbonilo (-C(=O)-), o tio-carbonilo (-C(=S)-);

o una sal farmacéuticamente aceptable del mismo,

en la preparación de una formulación farmacéutica para el tratamiento de una enfermedad que dependa de la actividad de la renina.

3. El uso de acuerdo con la reivindicación 1, o de acuerdo con la reivindicación 2, en donde la enfermedad que se va a tratar es hipertensión.

4. Un compuesto de la fórmula I:



(I)

en donde:

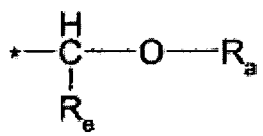
R^1 es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, alquenilo insustituido o sustituido, alquinilo sustituido o insustituido, o acilo;

R^2 es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico

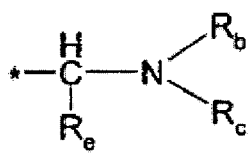
insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo monocíclico-alquilo sustituido o arilo bicíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, alquenilo insustituido o sustituido, o alquinilo insustituido o sustituido; con la condición de que, si R^1 es una de las fracciones mencionadas en la definición de R^1 diferente de acilo, entonces R^2 también puede ser arilo monocíclico-alquilo insustituido;

R^3 es una fracción seleccionada a partir del grupo de fracciones de las fórmulas:

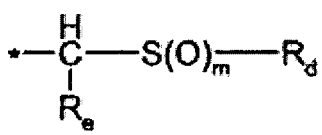
(a)



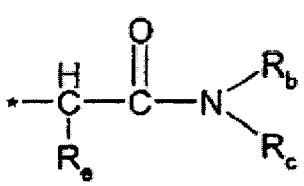
(b)



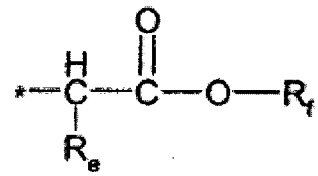
(c)



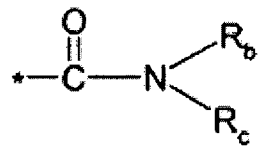
(d)



(e)

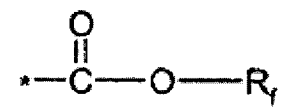


(f)



y

(g)



en donde, en cualquiera de las fracciones de las fórmulas dadas anteriormente bajo (a), (b), (c), (d), (e), (f), y (g), el asterisco (*) muestra el enlace que enlaza a la fracción R^3 respectiva con el resto de la molécula en la Fórmula I,

R_a es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, acilo, o hidrógeno;

R_b y R_c se seleccionan independientemente a partir del grupo que consiste en alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico

insustituido o sustituido, arilo bicíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, acilo, o hidrógeno, con la condición de que, de preferencia, no más de uno de R_b y R_c sea acilo, y con la condición de que, si R_c es una de las fracciones mencionadas diferente de acilo, entonces R_b también puede ser arilo monocíclico-alquilo insustituido o sustituido; o R_b y R_c pueden formar juntos un anillo de 3 a 7 miembros que contenga nitrógeno, el cual puede estar insustituido o sustituido;

R_d es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, o acilo, o puede tener uno de estos significados, o puede ser $-N(R_b(R_c)$ si **m** es 1 ó de preferencia 2;

R_e es hidrógeno, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, o alquilo de 1 a 7 átomos de carbono sustituido o de preferencia insustituido; y

R_f es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico

insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido;

m es 0, 1, ó 2;

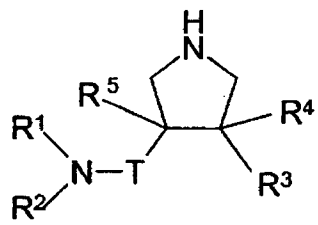
cada uno de R^4 y R^5 se selecciona, independiente-mente uno del otro, a partir de hidrógeno, alquilo insustituido o sustituido, hidroxi, o hidroxi esterificado o eterificado;

y T es metileno, metileno mono-sustituido por alquilo, o es carbonilo, o tio-carbonilo;

o una sal farmacéuticamente aceptable del mismo,

para utilizarse en el tratamiento de un mamífero.

5. Un compuesto de la fórmula I:



(I)

en donde:

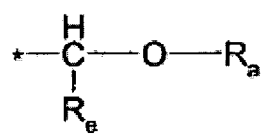
R^1 es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o

sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, alquenilo insustituido o sustituido, alquinilo sustituido o insustituido, o acilo;

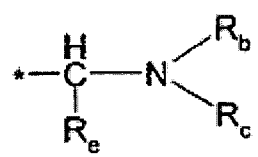
R^2 es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo bicíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, alquenilo insustituido o sustituido, o alquinilo insustituido o sustituido; con la condición de que, si R^1 es una de las fracciones mencionadas en la definición de R^1 diferente de acilo, entonces R^2 también puede ser arilo monocíclico-alquilo insustituido o sustituido;

R^3 es una fracción seleccionada a partir del grupo de fracciones de las fórmulas:

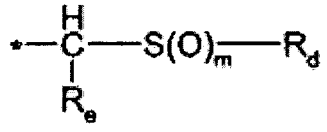
(a)



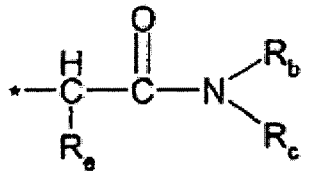
(b)



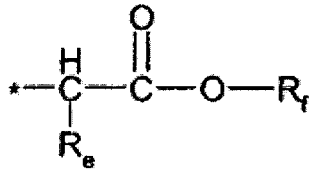
(c)



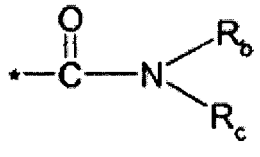
(d)



(e)

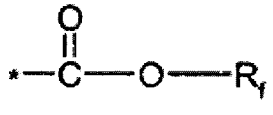


(f)



y

(g)



en donde, en cualquiera de las fracciones de las fórmulas dadas anteriormente bajo (a), (b), (c), (d), (e), (f), y (g), el asterisco (*) muestra el enlace que enlaza a la fracción R^3 respectiva con el resto de la molécula en la Fórmula I,

R_a es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o

sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, acilo, o hidrógeno;

R_b y R_c se seleccionan independientemente a partir del grupo que consiste en alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo bicíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, acilo, o hidrógeno, con la condición de que, de preferencia, no más de uno de R_b y R_c sea acilo, y con la condición de que, si R_c es una de las fracciones mencionadas diferente de acilo, entonces R_b también puede ser arilo monocíclico-alquilo insustituido o sustituido; o R_b y R_c pueden formar juntos un anillo de 3 a 7 miembros que contenga nitrógeno, el cual puede estar insustituido o sustituido;

R_d, en una fracción de las fórmulas (c) ó (e), es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, o acilo, o puede tener uno de estos significados, o puede ser $-N(R_b(R_c)$ si **m** es 1 ó de

preferencia 2;

R_e es hidrógeno, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, o alquilo de 1 a 7 átomos de carbono sustituido o de preferencia insustituido; y

R_f es alquilo sustituido o de preferencia arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido;

m es 0, 1, ó 2;

cada uno de R^4 y R^5 se selecciona, independiente-mente uno del otro, a partir de hidrógeno, alquilo insustituido o sustituido, hidroxi, o hidroxi esterificado o eterificado;

y T es metileno, metileno mono-sustituido por alquilo, carbonilo, o tio-carbonilo;

o una sal del mismo.

6. Un compuesto de la Fórmula I de acuerdo con la reivindicación 5,

en donde:

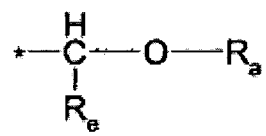
R^1 es acilo;

R^2 es cicloalquilo insustituido o sustituido, o de preferencia

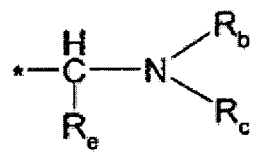
alquilo insustituido o sustituido,

R^3 es una fracción seleccionada a partir del grupo de fracciones de las fórmulas:

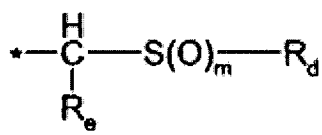
(a)



(b)

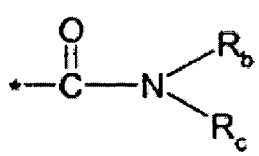


(c)



y

(f)



en donde, en cualquiera de las fracciones de las fórmulas dadas anteriormente bajo (a), (b), (c), y (f), el asterisco (*) muestra el enlace que enlaza a la fracción R^3 respectiva con el resto de la molécula en la Fórmula I;

R_a es acilo o hidrógeno;

R_b es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo de

1 a 7 átomos de carbono insustituido o sustituido, o acilo;

R_c es hidroxi-alquilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, o de preferencia cicloalquilo de 3 a 8 átomos de carbono, hidrógeno, o alquilo de 1 a 7 átomos de carbono;

R_d es arilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido;

R_e es hidrógeno (preferido) o alquilo de 1 a 7 átomos de carbono; y

m es 2;

cada uno de R^4 y R^5 se selecciona, independiente-mente uno del otro, a partir de hidrógeno, alquilo insustituido o sustituido, hidroxi, o hidroxi esterificado o eterificado;;

y T es metileno, metileno mono-sustituido por alquilo, carbonilo, o tio-carbonilo;

o una sal (en especial farmacéuticamente aceptable) del mismo.

7. El uso de acuerdo con cualquiera de las reivindicaciones 1 a 3, el compuesto de la Fórmula I o una sal farmacéuticamente aceptable del mismo para utilizarse de acuerdo con la reivindicación 4, o el compuesto de la Fórmula I o una sal del mismo de acuerdo con cualquiera de las reivindicaciones 5 ó 6, en donde una o más, de preferencia todas las definiciones de sustituyentes y símbolos, donde se mencionan, son como sigue:

"de 1 a 7 átomos de carbono" define una fracción con hasta

e incluyendo máximo 7, en especial hasta e incluyendo máximo 4 átomos de carbono, estando esta fracción ramificada una o más veces, o de una sola cadena y enlazada por medio de un átomo de carbono terminal o no terminal, por ejemplo, alquilo de 1 a 7 átomos de carbono es pentilo normal, hexilo normal, o heptilo normal, o de preferencia alquilo de 1 a 4 átomos de carbono, en especial metilo, etilo, propilo normal, propilo secundario, butilo normal, isobutilo, butilo secundario, butilo terciario;

halo o halógeno es flúor, cloro, bromo o yodo, más preferiblemente flúor, cloro o bromo;

arilo mono- o bi-cíclico insustituido o sustituido es un arilo mono- o bi-cíclico con 6 a 22 átomos de carbono, en donde uno de los anillos del arilo bicíclico puede ser un anillo parcial o completamente saturado condensado al otro anillo aromático, en especial fenilo, indanilo, indenilo, 1,2,3,4-tetrahidro-naftilo, o naftilo, y está insustituido o sustituido por una o más, en especial por una a tres fracciones, de preferencia independientemente seleccionadas a partir del grupo que consiste en:

un sustituyente de la Fórmula -(alquileno de 0 a 7 átomos de carbono)-$(X)_r$-(alquileno de 1 a 7 átomos de carbono)-$(Y)_s$-(alquileno de 0 a 7 átomos de carbono)-H (en especial en arilo sustituido o aril-alquilo sustituido como R^1), en donde alquileno de 0 átomos de carbono significa que está presente un enlace en lugar de alquileno enlazado, y alquileno en cada caso puede ser de cadena recta o ramificada, y puede estar insustituido o (con

menor preferencia) sustituido, por ejemplo, por una o más fracciones como se definen para alquilo sustituido, en especial por halógeno, especialmente flúor, hidroxi, alcoxilo de 1 a 7 átomos de carbono, feniloxilo, naftiloxilo, alcanoiloxilo de 1 a 7 átomos de carbono, benzoiloxilo, naftoiloxilo, amino, mono- o di-(alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono, fenil-alcanoílo de 1 a 7 átomos de carbono, naftil-alcanoílo de 1 a 7 átomos de carbono, fenilo, naftilo, fenil-alquilo de 1 a 7 átomos de carbono, y/o naftil-alquilo de 1 a 7 átomos de carbono)-amino, carboxilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, o ciano; **r** y **s**, cada uno independiente-mente del otro, son 0 ó 1, y cada uno de X e Y, si están presentes e independientemente de los otros, es -O-, -NV-, -S-, -O-CO-, -CO-O-, -NV-CO-; -CO-NV-; -NV-SO_2-; -SO_2-NV; -NV-CO-NV-, -NV-CO-O-, -O-CO-NV-, -NV-SO_2-NV-, en donde V es hidrógeno o alquilo insustituido o sustituido como se define más adelante, en especial alquilo de 1 a 7 átomos de carbono, o es fenilo, naftilo, fenil- o naftil-alquilo de 1 a 7 átomos de carbono, o halo-alquilo de 1 a 7 átomos de carbono; por ejemplo, el sustituyente de esta fórmula es alquilo de 1 a 7 átomos de carbono, tal como metilo, etilo, propilo normal, isopropilo, butilo normal, isobutilo, butilo secundario, o butilo terciario, halo-alquilo de 1 a 7 átomos de carbono, tal como trifluorometilo, hidroxi-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, tal como 3-metoxi-propilo ó 2-metoxi-etilo, alcoxilo de 1 a 7

átomos de carbono-alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, feniloxi- o naftiloxi-alquilo de 1 a 7 átomos de carbono, alcanoiloxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, amino-alquilo de 1 a 7 átomos de carbono, tal como amino-metilo, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-amino-alquilo de 1 a 7 átomos de carbono, mono- o di- (alquilo de 1 a 7 átomos de carbono, naftil, fenil, naftil-alquilo de 1 a 7 átomos de carbono, y/o fenil-alquilo de 1 a 7 átomos de carbono)-amino-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono-amino-alquilo de 1 a 7 átomos de carbono, alquilo de 1 a 7 átomos de carbono-O-CO-NH-alquilo de 1 a 7 átomos de carbono, alquilo de 1 a 7 átomos de carbono-sulfonil-amino-alquilo de 1 a 7 átomos de carbono, alquilo de 1 a 7 átomos de carbono-NH-CO-NH-alquilo de 1 a 7 átomos de carbono, alquilo de 1 a 7 átomos de carbono-NH-SO_2-NH-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono, hidroxi-alcoxilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono, alcanoiloxilo de 1 a 7 átomos de carbono, halo-alcoxilo de 1 a 7 átomos de carbono, tal como fluoro-metoxilo, fenil- o naftil-alcanoiloxilo de 1 a 7 átomos de carbono, fenil- o naftil-alquilo de 1 a 7 átomos de carbono-amino-carboniloxilo, halo-tioalquilo de 1 a 7 átomos de carbono, tal como trifluoro-tiometilo, fenil- o naftil-tioalquilo de 1 a 7 átomos de carbono, mono- o di-(alquilo de 1 a 7 átomos de carbono-, naftil-alquilo de 1 a 7

átomos de carbono-, fenil-alquilo de 1 a 7 átomos de carbono-, y/o alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-)amino, alcanoílo de 1 a 7 átomos de carbono-amino, alquilo de 1 a 7 átomos de carbono-sulfonil-amino, fenil- o naftil-alcanoílo de 1 a 7 átomos de carbono-amino, fenil- o naftil-alquilo de 1 a 7 átomos de carbono-amino-carbonil-amino, carboxi-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-carbonilo, hidroxi-alcoxilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono-carbonilo, amino-alcoxilo de 1 a 7 átomos de carbono-carbonilo, (N-) mono-(alquilo de 1 a 7 átomos de carbono)-amino-alcoxilo de 1 a 7 átomos de carbono-carbonilo, alcanoílo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono-carbonilo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, naftil-alquilo de 1 a 7 átomos de carbono, y/o fenil-alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, alquilo de 1 a 7 átomos de carbono-sulfonilo, halo-alquilo de 1 a 7 átomos de carbono-sulfonilo, hidroxi-alquilo de 1 a 7 átomos de carbono-sulfonilo, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-sulfonilo, amino-alquilo de 1 a 7 átomos de carbono-sulfonilo, N-mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino-alquilo de 1 a 7 átomos de carbono-sulfonilo, alcanoílo de 1 a 7 átomos de carbono-amino-alquilo de 1 a 7 átomos de carbono-sulfonilo, N-alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-carbamoílo, o N-mono- o N,N-di-(alquilo de 1 a

7 átomos de carbono)-amino-sulfonilo;

a partir de alquenilo de 2 a 7 átomos de carbono, alquinilo de 2 a 7 átomos de carbono, fenilo, naftilo, hetero-ciclilo mono- o bi-cíclico, en especial como se define más adelante para heterociclilo mono- o bi-cíclico, de preferencia seleccionado a partir de pirrolilo, furanilo, tienilo, pirimidin-2,4-dion-1-, -3-, ó -5-ilo y tetrahidrofuranilo, fenil- o naftil-, o (heterociclilo mono- o bi-cíclico)-alquilo de 1 a 7 átomos de carbono o alquiloxilo de 1 a 7 átomos de carbono, en donde heterociclilo mono- o bi-cíclico es como se define más adelante, de preferencia seleccionado a partir de pirrolilo, furanilo, tetrahidrofuranilo, tetrahidropiranilo, y tienilo; tal como bencilo o naftil-metilo, tetrahidro-furanil- o tetrahidro-piranil-alquiloxilo de 1 a 7 átomos de carbono-carbonilo, benzoil- o naftoil-amino-alquilo de 1 a 7 átomos de carbono, (fenil- o naftil- o heterociclilo mono- o bi-cíclico)-sulfonil-amino-alquilo de 1 a 7 átomos de carbono, en donde fenilo o naftilo o heterociclilo mono- o bi-cíclico está insustituido o sustituido, de preferencia por una o más, en especial por una a tres fracciones de alquilo de 1 a 7 átomos de carbono, (fenil o naftil o heterociclilo mono- o bi-cíclico)-alquilo de 1 a 7 átomos de carbono-sulfonil-amino-alquilo de 1 a 7 átomos de carbono, halógeno, hidroxi, fenil-alcoxilo de 1 a 7 átomos de carbono en donde el fenilo está de preferencia insustituido o sustituido, de preferencia por alcoxilo de 1 a 7 átomos de carbono y/o halógeno, heterociclilo mono- o bi-cíclico-

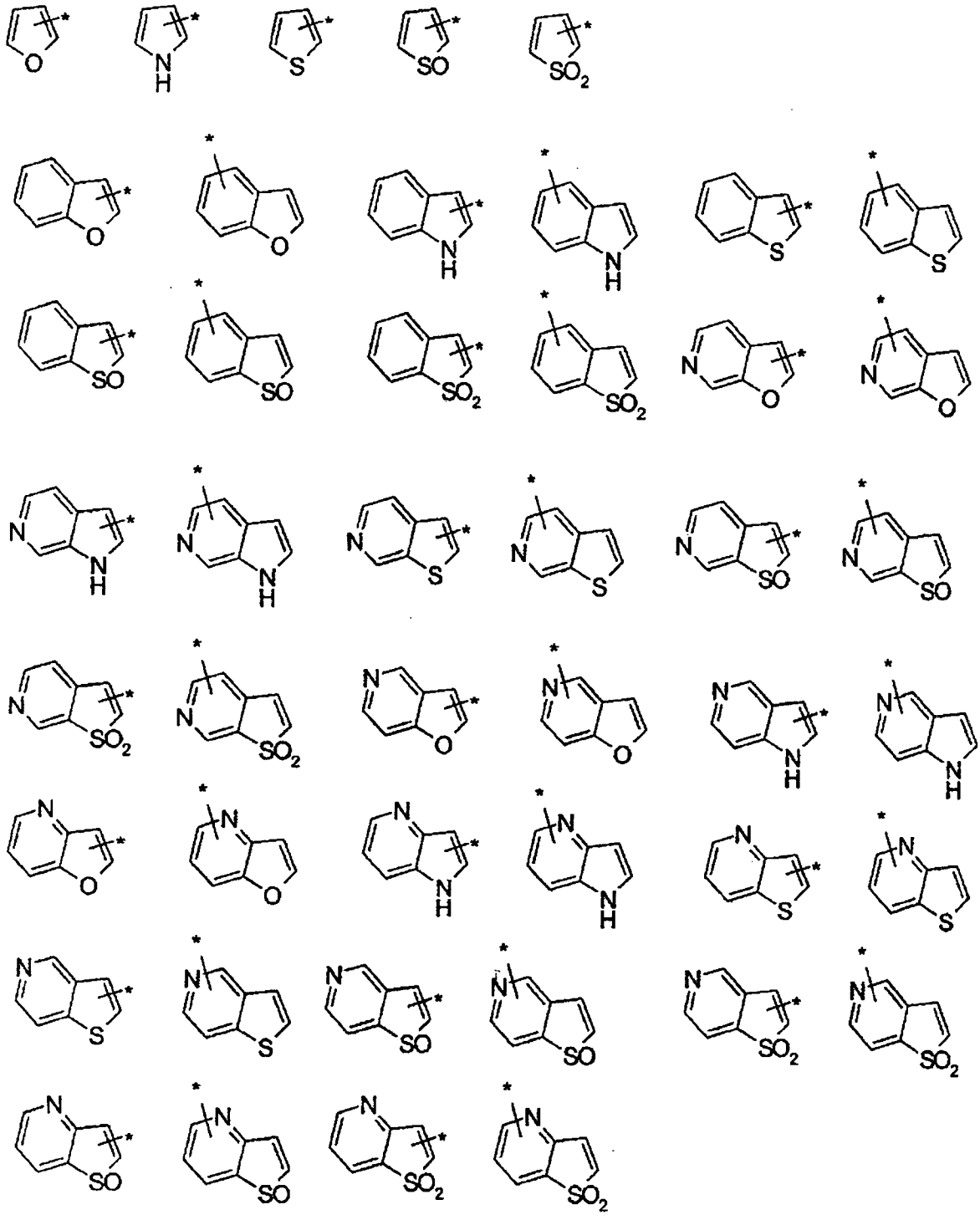
alcoxilo de 1 a 7 átomos de carbono, (heterociclilo mono- o bi-cíclico o fenil o naftil)-oxilo, naftil-alquiloxilo de 1 a 7 átomos de carbono, (benzoil o naftoil o heterociclilo mono- o bi-cíclico-carbonil)-oxilo, (fenil o naftil o hetero-ciclilo mono- o bi-cíclico)-amino-carboniloxilo, (fenil o naftil o heterociclilo mono- o bi-cíclico)-tio, (benzoil o naftoil o heterociclilo mono- o bi-cíclico)-tio, nitro, amino, di-((naftil o fenil o heterociclilo mono- o bi-cíclico)-alquilo de 1 a 7 átomos de carbono)-amino, (benzoil o naftoil o heterociclilo mono- o bi-cíclico)-amino, (fenil o naftil o heterociclilo mono- o bi-cíclico)-sulfonil-amino, en donde el fenilo o naftilo está insustituido o sustituido, de preferencia por una o más, en especial por una a tres fracciones de alquilo de 1 a 7 átomos de carbono, (fenil o naftil o heterociclilo mono- o bi-cíclico)-alquilo de 1 a 7 átomos de carbono-sulfonil-amino, (fenil o naftil o heterociclilo mono- o bi-cíclico)-amino-carbonil-amino, (fenil o naftil o heterociclilo mono- o bi-cíclico)-oxicarbonil-amino, (fenil o naftil o heterociclilo mono- o bi-cíclico)-alquiloxilo de 1 a 7 átomos de carbono-carbonil-amino, carboxilo, alquilo de 1 a 7 átomos de carbono-carbonilo, halo-alquilo de 1 a 7 átomos de carbono-carbonilo, hidroxi-alquilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-carbonilo, amino-alquilo de 1 a 7 átomos de carbono-carbonilo, (N-) mono- o (N,N-) di-(alquilo de 1 a 7 átomos de carbono)-amino-alquilo de 1 a 7 átomos de carbono-carbonilo, alcanoílo de 1 a 7 átomos de carbono-amino-alquilo de 1 a 7

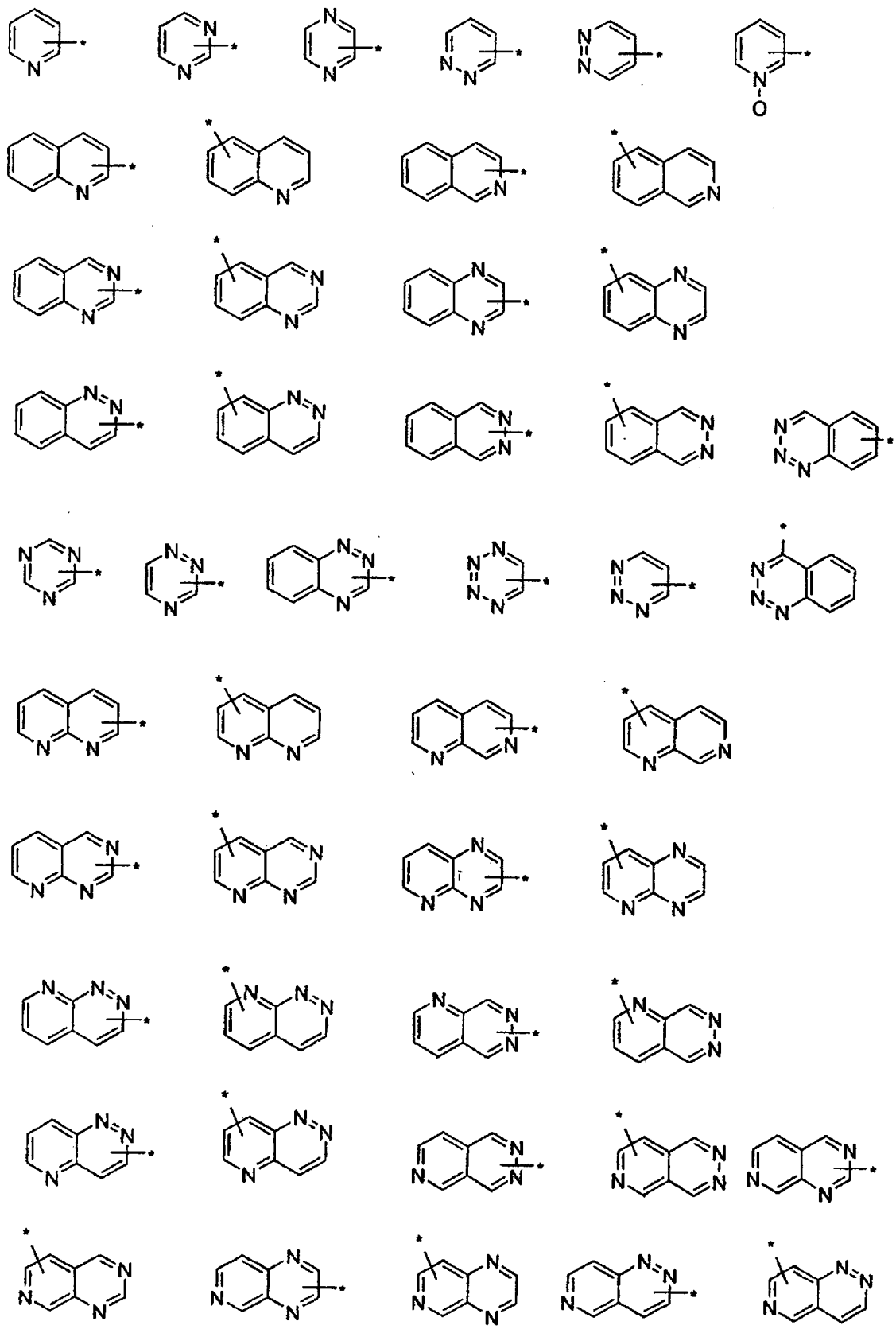
átomos de carbono-carbonilo, halo-alcoxilo de 1 a 7 átomos de carbono-carbonilo, (fenil o naftil o heterociclilo mono- o bi-cíclico)-oxi-carbonilo, (fenil o naftil o heterociclilo mono- o bi-cíclico)-alcoxilo de 1 a 7 átomos de carbono-carbonilo, (N,N-) di-(alquilo de 1 a 7 átomos de carbono)-amino-alcoxilo de 1 a 7 átomos de carbono-carbonilo, carbamoílo, N-mono- o N,N-di-(naftil o fenil o heterociclilo mono- o bi-cíclico)-amino-carbonilo, ciano, alquileno de 1 a 7 átomos de carbono que está insustituido o sustituido por hasta cuatro sustituyentes de alquilo de 1 a 7 átomos de carbono, y enlazado a dos átomos adyacentes del anillo de la fracción de arilo, sulfenilo, sulfinilo, alquilo de 1 a 7 átomos de carbono-sulfinilo, (fenil o naftil o heterociclilo mono- o bi-cíclico)-sulfinilo en donde el fenilo o naftilo está insustituido o sustituido de preferencia por una o más, en especial por una a tres fracciones de alquilo de 1 a 7 átomos de carbono, fenil- o naftil-alquilo de 1 a 7 átomos de carbono-sulfinilo, sulfonilo, (fenil o naftil o heterociclilo mono- o bi-cíclico)-sulfonilo en donde el fenilo o naftilo está insustituido o sustituido de preferencia por una o más, en especial por una a tres fracciones de alquilo de 1 a 7 átomos de carbono, (fenil o naftil o heterociclilo mono- o bi-cíclico)-alquilo de 1 a 7 átomos de carbono-sulfonilo, sulfamoílo, y N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, fenil, naftil, heterociclilo mono- o bi-cíclico, fenil-alquilo de 1 a 7 átomos de carbono, naftil-alquilo de 1 a 7 átomos de carbono, y/o heterociclilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono)-amino-sulfonilo;

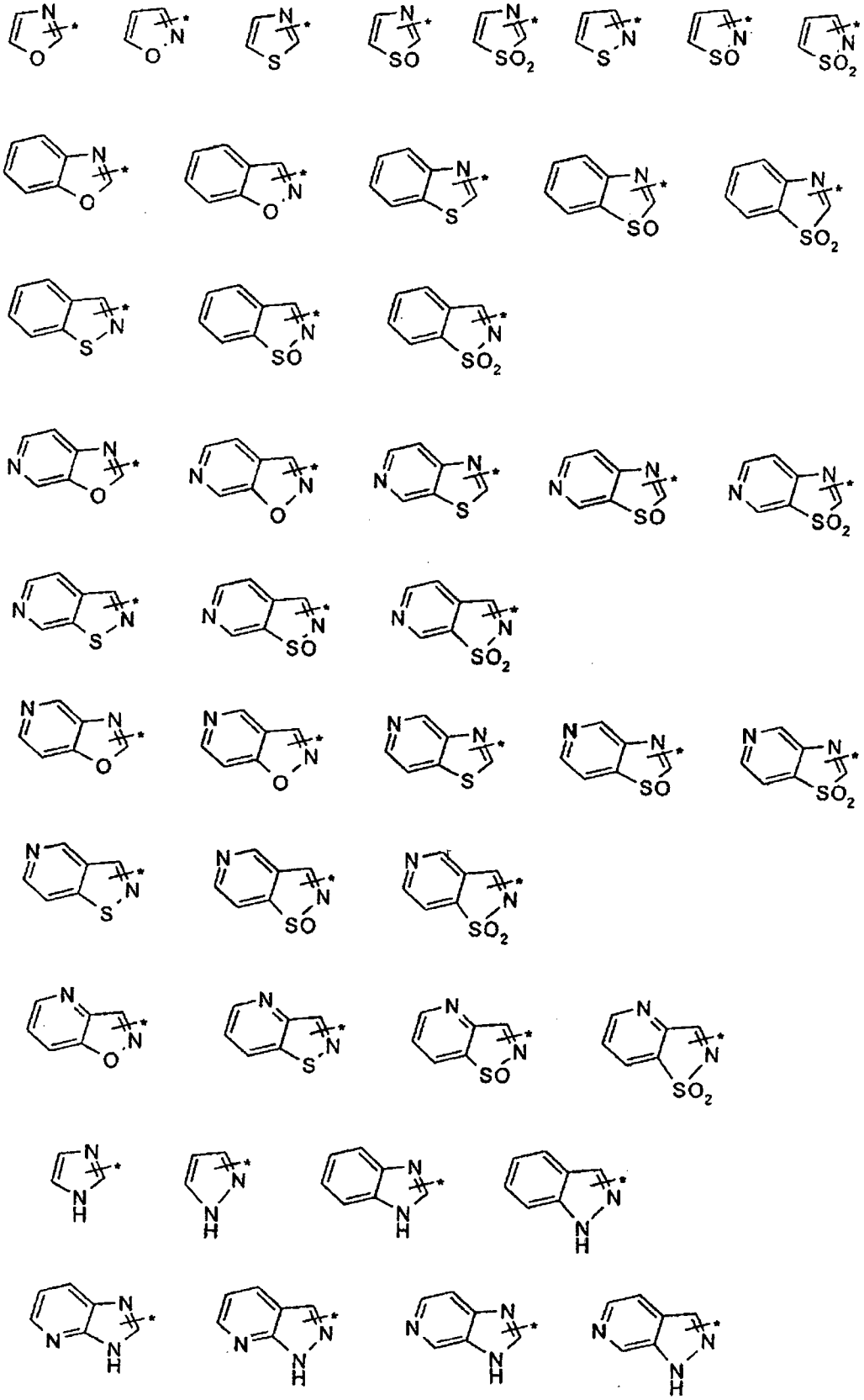
en donde cualquier fenilo o naftilo o heterociclilo mono- o bi-cíclico (cuyo heterociclilo mono- o bi-cíclico de preferencia es como se define para heterociclilo mono- o bi-cíclico, más preferiblemente se selecciona a partir de pirrolilo, furanilo, tetrahidrofuranilo, tetrahidropiranilo, y tienilo), mencionado como sustituyente de, o como parte de un sustituyente de arilo sustituido, está insustituido o sustituido por una o más, de preferencia hasta tres fracciones independientemente seleccionadas a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono, alquenilo de 1 a 7 átomos de carbono, alquinilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, tal como trifluoro-metilo, halógeno, en especial flúor, cloro, bromo o yodo, hidroxi, alcoxilo de 1 a 7 átomos de carbono, feniloxilo, naftiloxilo, fenil- o naftil-alcoxilo de 1 a 7 átomos de carbono, alcanoiloxilo de 1 a 7 átomos de carbono, fenil- o naftil-alcanoiloxilo de 1 a 7 átomos de carbono, amino, mono- o di-(alquilo de 1 a 7 átomos de carbono, fenil, naftil, fenil-alquilo de 1 a 7 átomos de carbono, naftil-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono, y/o fenil- o naftil-alcanoílo de 1 a 7 átomos de carbono)-amino, carboxilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, fenoxi-carbonilo, naftiloxi-carbonilo, fenil-alquiloxilo de 1 a 7 átomos de carbono-carbonilo, naftil-alcoxilo de 1 a 7 átomos de carbono-carbonilo, carbamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, fenil, naftil, fenil-alquilo de 1 a 7 átomos de carbono, y/o naftil-alquilo de 1 a 7

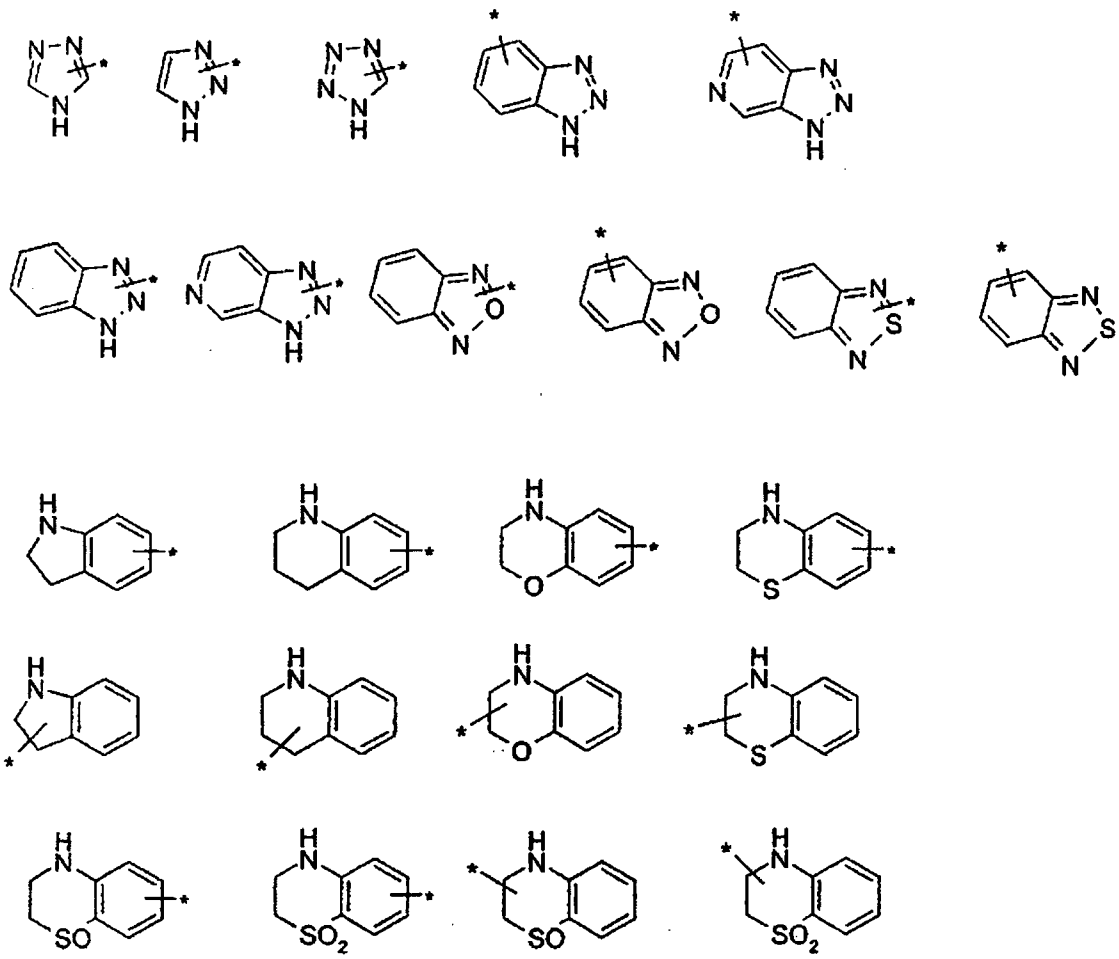
átomos de carbono)-amino-carbonilo, ciano, sulfo, sulfamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, fenil, naftil, fenil-alquilo de 1 a 7 átomos de carbono, y/o naftil-alquilo de 1 a 7 átomos de carbono)-amino-sulfonilo, y nitro, o de preferencia, en donde se mencionan los sustituyentes preferidos, por uno o más de estos sustituyentes mencionados;

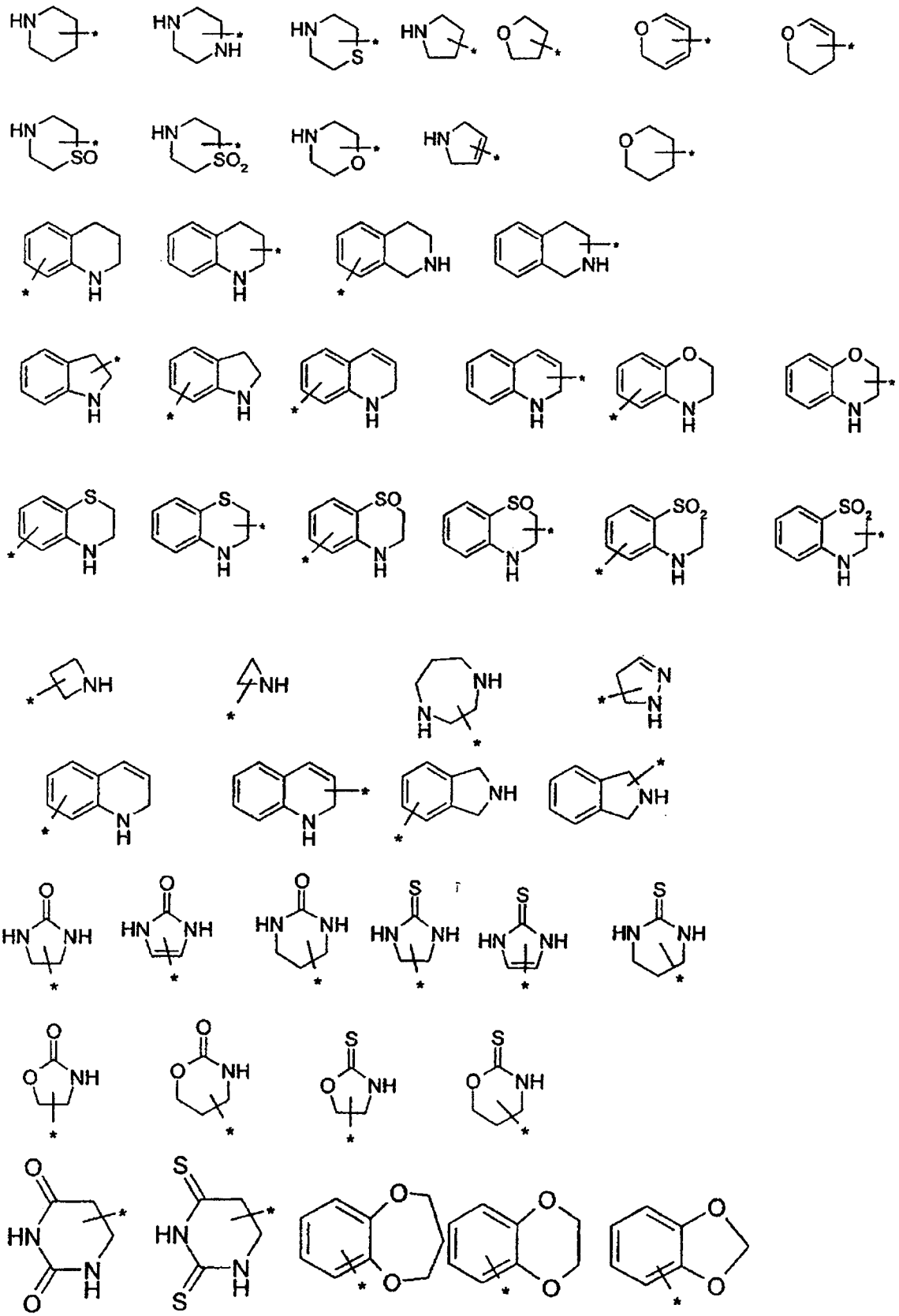
heterociclilo mono- o bi-cíclico insustituido o sustituido es una fracción heterocíclica mono- o bi-cíclica con un sistema de anillo insaturado, parcialmente saturado, o saturado, de preferencia con 3 a 22, más preferiblemente 3 a 14 átomos del anillo, y con uno o más, de preferencia de uno a cuatro heteroátomos independientemente seleccionados a partir de nitrógeno, oxígeno, y azufre, que está insustituido o sustituido por uno o más, por ejemplo hasta tres sustituyentes de preferencia independientemente seleccionados a partir de los sustituyentes mencionados anteriormente para arilo, y a partir de oxo (=O), imino (=NR), en donde R puede ser alquilo de 1 a 7 átomos de carbono o hidrógeno, y tioxo (=S), de preferencia oxo (=O) y tioxo (=S), en donde, de una manera preferible, heterociclilo mono- o bi-cíclico insustituido o sustituido se selecciona a partir de las siguientes fracciones:

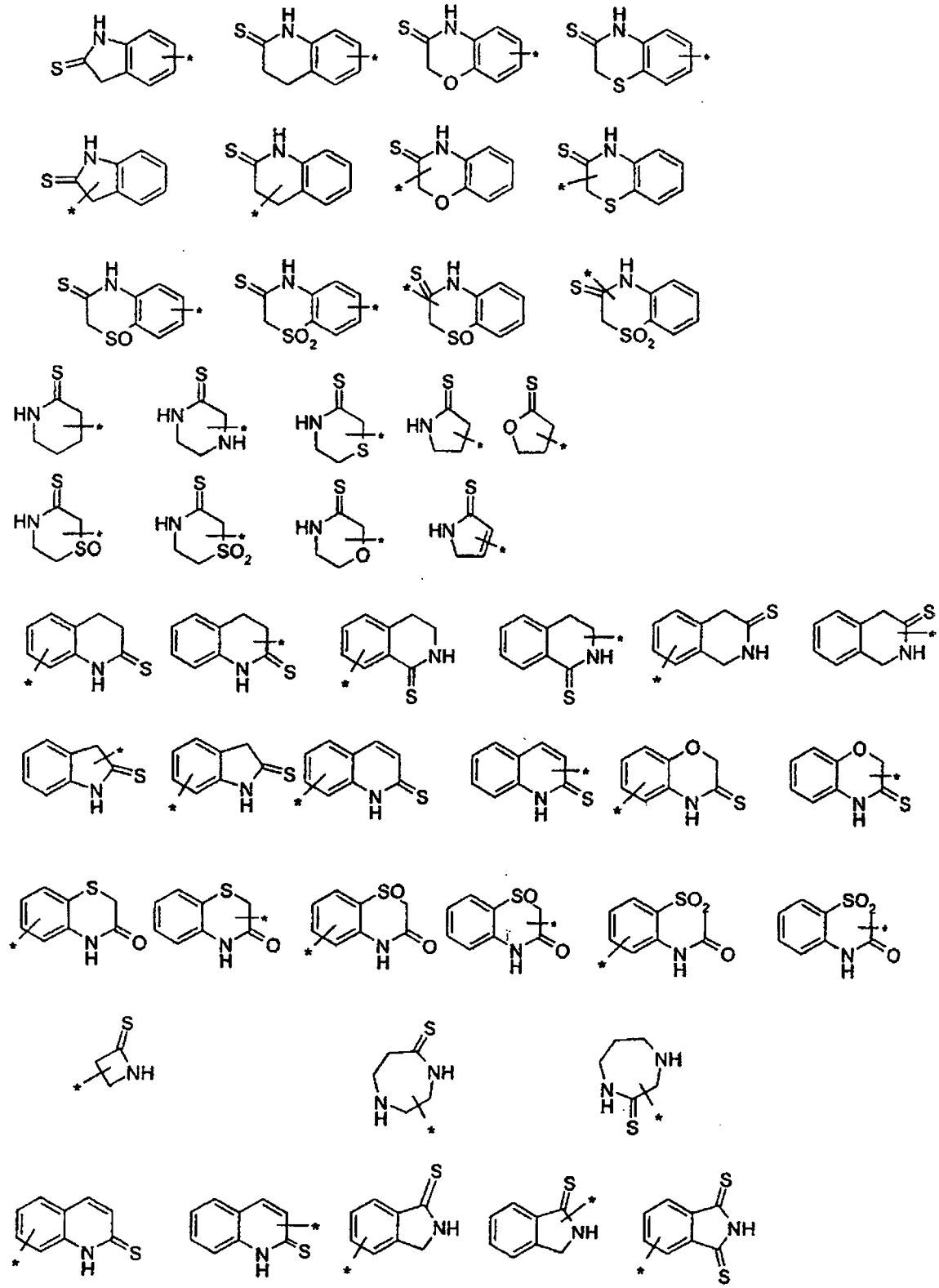

O
NH
S
SO
SO2
N
O
NH
S
SO
SO2
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S
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SO2
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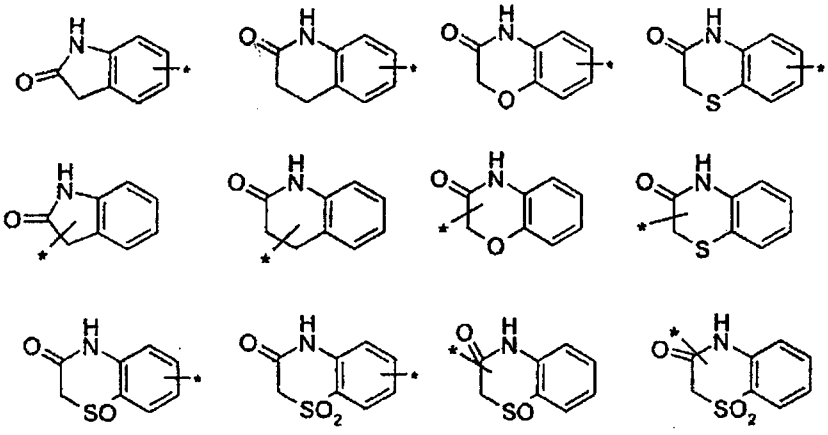


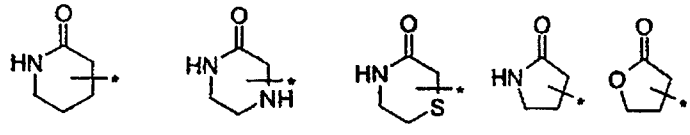


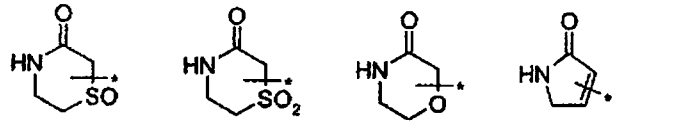


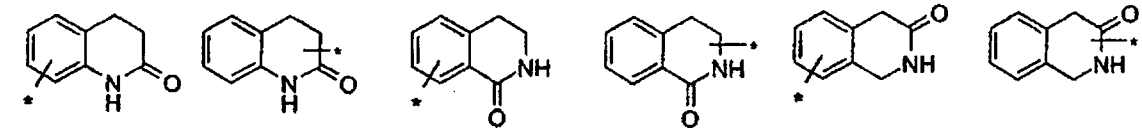


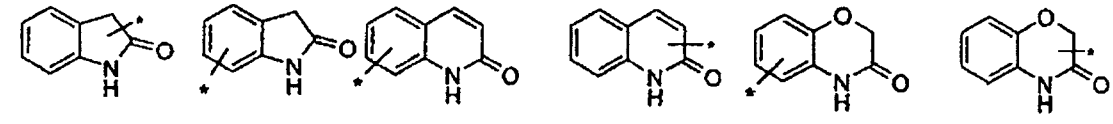


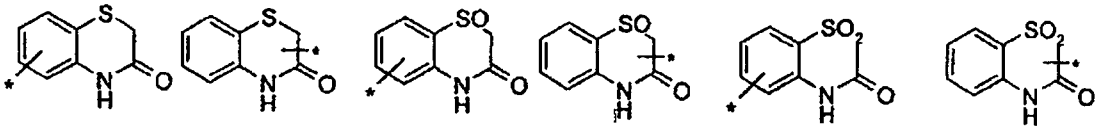




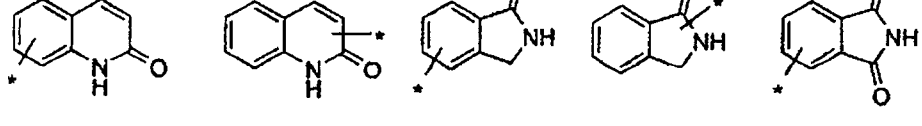












en donde, en cada caso en donde esté presente un NH, y el enlace con el asterisco que conecta a la fracción de heterociclilo respectiva con el resto de la molécula, el H puede ser reemplazado con este enlace, y/o el H puede ser reemplazado por un sustituyente (formando de esta manera imino sustituido), y puede haber uno o más sustituyentes como justamente se describió;

cicloalquilo mono- o bi-cíclico insustituido o sustituido es cicloalquilo mono- o bi-cíclico, más preferiblemente mono-cíclico, de 3 a 16 átomos de carbono, más preferiblemente de 3 a 10 átomos de carbono, el cual puede incluir uno o más dobles (por ejemplo en cicloalquenilo) y/o triples enlaces (por ejemplo en ciclo-alquinilo) con menos dobles y/o triples enlaces que los requeridos para formar un sistema de anillo completamente insaturado; en donde de preferencia, el ciclo-alquilo mono- o bi-cíclico está saturado; y en donde el cicloalquilo mono- o bi-cíclico está insustituido o sustituido por uno o más, por ejemplo por uno a tres sustituyentes de preferencia independientemente seleccionados a partir de aquéllos mencionados anteriormente como sustituyentes para arilo;

en arilo mono- o bi-cíclico-alquilo o -alquilo de 1 a 7 átomos de carbono insustituido o sustituido, el arilo mono- o bi-cíclico, el cual está insustituido o sustituido por uno o más sustituyentes, por ejemplo por uno a tres sustituyentes independientemente seleccionados a partir de aquéllos mencionados anteriormente como sustituyentes para arilo, y el arilo está enlazado a alquilo, de

preferencia alquilo de 1 a 7 átomos de carbono, ya sea terminalmente o bien en cualquier otro átomo de carbono de la cadena de alquilo, por ejemplo en el átomo de carbono en la posición 1; en donde el alquilo de 1 a 7 átomos de carbono está de otra manera insustituido o sustituido como se describe más adelante para alquilo insustituido o sustituido y/o con arilo mono- o bi-cíclico insustituido o sustituido como se describe en lo anterior;

en heterociclilo mono- o bi-cíclico-alquilo o -alquilo de 1 a 7 átomos de carbono, el heterociclilo mono- o bi-cíclico es de preferencia como se describe anteriormente, y está insustituido o sustituido por uno o más, por ejemplo hasta tres sustituyentes independientemente seleccionados a partir de aquéllos mencionados en lo anterior para arilo sustituido, y a partir de oxo (=O), imino (=NR), en donde R puede ser alquilo de 1 a 7 átomos de carbono o hidrógeno, y tioxo (=S), de preferencia oxo (=O) y tioxo (=S), y el heterociclilo está enlazado a alquilo, de preferencia alquilo de 1 a 7 átomos de carbono, ya sea terminalmente o bien en cualquier otro átomo de carbono de la cadena de alquilo, por ejemplo en el átomo de carbono en la posición 1; en donde el alquilo de 1 a 7 átomos de carbono está de otra manera insustituido o sustituido como se describe más adelante para alquilo insustituido o sustituido y/o con arilo mono- o bi-cíclico insustituido o sustituido como se describe en lo anterior;

en cicloalquilo mono- o bi-cíclico-alquilo o -alquilo de 1 a 7 átomos de carbono, el cicloalquilo mono- o bi-cíclico es de preferencia como se describe anteriormente, y está insustituido o sustituido por uno o más, por ejemplo hasta tres sustituyentes independientemente seleccionados a partir de aquéllos mencionados en lo anterior para arilo sustituido, y el cicloalquilo está enlazado a alquilo, de preferencia alquilo de 1 a 7 átomos de carbono, ya sea terminalmente o bien en cualquier otro átomo de carbono de la cadena de alquilo, por ejemplo en el átomo de carbono en la posición 1; en donde el alquilo de 1 a 7 átomos de carbono está de otra manera insustituido o sustituido como se describe más adelante para alquilo insustituido o sustituido y/o con arilo mono- o bi-cíclico insustituido o sustituido como se describe en lo anterior;

acilo es de preferencia arilo mono- o bi-cíclico-carbonilo o -sulfonilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-carbonilo o -sulfonilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-carbonilo o -sulfonilo insustituido o sustituido, formilo o (alquilo insustituido o sustituido, arilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, o cicloalquilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido)-carbonilo o -sulfonilo, o - en especial si está enlazado con N, S, u O -. alquiloxi-carbonilo insustituido o sustituido, arilo mono- o bi-cíclico-oxi-carbonilo

insustituido o sustituido, heterociclilo mono- o bi-cíclico-oxicarbonilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-oxicarbonilo insustituido o sustituido, arilo mono- o bi-cíclico-oxilo de 1 a 7 átomos de carbono-carbonilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-oxilo de 1 a 7 átomos de carbono-carbonilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-oxilo de 1 a 7 átomos de carbono-carbonilo insustituido o sustituido, o N-mono- o N,N-di-(arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, y/o alquilo insustituido o sustituido)-amino-carbonilo o -amino-sulfonilo, con la condición de que la fracciones enlazadas con -oxicarbonilo de preferencia estén enlazadas a un átomo de nitrógeno en el resto de la molécula; en donde las fracciones de acilo preferidas diferentes de R^1 y/o R^2, donde se mencionen, son alcanoílo de 1 a 7 átomos de carbono, fenil-alcanoílo de 1 a 7 átomos de carbono insustituido (o mono-, di-, o tri-sustituido por (halógeno, alcoxilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono-alquiloxilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, y/o alquilo de 1 a 7 átomos de carbono)), ciclo-alquilo de

3 a 8 átomos de carbono-carbonilo, (tetra-hidrofuranil o tetra-hidropiranil)-carbonilo o (tetrahidro-furanil o tetrahidropiranil)-alquilo de 1 a 7 átomos de carbono-carbonilo, (fenil- o fenil-alquilo de 1 a 7 átomos de carbono)-sulfonilo insustituido o mono-, di-, o tri-sustituido por (halógeno y/o alquilo de 1 a 7 átomos de carbono), alquilo de 1 a 7 átomos de carbono-sulfonilo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, N-[fenilo o fenil-alquilo de 1 a 7 átomos de carbono]-amino-carbonilo, N-[cicloalquilo de 3 a 8 átomos de carbono o cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono]-amino-carbonilo, alquilo de 1 a 7 átomos de carbono-amino-carbonilo, N-(fenil-alquilo de 1 a 7 átomos de carbono)-(alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, N-(fenil-alquilo de 1 a 7 átomos de carbono)-(cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, N-(alquilo de 1 a 7 átomos de carbono)-(cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, N-(fenil-alquilo de 1 a 7 átomos de carbono)-(cicloalquilo de 3 a 8 átomos de carbono)-amino-carbonilo, N-(heterociclil-alquilo de 1 a 7 átomos de carbono)-(cicloalquilo de 3 a 8 átomos de carbono)-amino-carbonilo, N-(heterociclil)-(cicloalquilo de 3 a 8 átomos de carbono)-amino-carbonilo, o (alquilo de 1 a 7 átomos de carbono, fenil, naftil, fenil-alquilo de 1 a 7 átomos de carbono, naftil-alquilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7

átomos de carbono, heterociclilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono, y/o heterociclilo mono- o bi-cíclico seleccionado de preferencia a partir de pirrolilo, furanilo, tienilo (= tiofenilo), tiazolilo, pirazolilo, triazolilo, tetrazolilo, oxetidinilo, 3-(alquilo de 1 a 7 átomos de carbono)-oxetidinilo, piridilo, pirimidinilo, morfolino, tiomorfolino, piperidinilo, piperazinilo, pirrolidinilo, 1H-indazanilo, benzo-furanilo, benzo-tiofenilo, (más preferiblemente) isoquinolinilo, quinolinilo, tetra-hidrofuran-onilo, tetrahidro-piranilo, e indolil)-oxicarbonilo, y (tetra-hidro-furanil o tetrahidro-piranil)-alquiloxilo de 1 a 7 átomos de carbono-carbonilo, mientras que, como acilo preferido como R^1 ó R^2, es indolil-alcanoílo de 1 a 7 átomos de carbono, -2,3-dihidro-benzo-[1,4]-dioxin-carbonilo, quinolil-alcanoílo de 1 a 7 átomos de carbono, o fenil-alcanoílo de 1 a 7 átomos de carbono, en donde indolilo, 2,3-dihidro-benzo-[1,4]-dioxina, quinolilo, y fenilo están insustituidos o sustituidos por un sustituyente de la Fórmula -(alquileno de 0 a 7 átomos de carbono)-$(X)_r$-(alquileno de 1 a 7 átomos de carbono)-$(Y)_s$-(alquileno de 0 a 7 átomos de carbono)-H, en donde alquileno de 0 átomos de carbono significa que está presente un enlace en lugar de alquileno enlazado, y alquileno puede ser en cada caso de cadena recta o ramificada, y puede estar insustituido, por ejemplo, por una o más fracciones como se definen para alquilo sustituido, en especial por halógeno, especialmente flúor, hidroxi, alcoxilo de 1 a 7 átomos de carbono, feniloxilo, naftiloxilo, alcanoiloxilo de 1 a 7 átomos de carbono,

benzoiloxilo, naftoiloxilo, amino, mono- o di-(alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono, fenilo, naftilo, fenil-alquilo de 1 a 7 átomos de carbono, y/o naftil-alquilo de 1 a 7 átomos de carbono)-amino, carboxilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, o ciano; **r** y **s**, cada uno independientemente del otro, son 0 ó 1, y cada uno de X e Y, si están presentes e independientemente de los otros, es -O-, -NV-, -S-, -O-CO-, -CO-O-, -NV-CO-; -CO-NV-; -NV-SO_2-; -SO_2-NV; -NV-CO-NV-, -NV-CO-O-, -O-CO-NV-, -NV-SO_2-NV-, en donde V es hidrógeno o alquilo insustituido o sustituido como se define más adelante, en especial alquilo de 1 a 7 átomos de carbono, o es fenilo, naftilo, fenil- o naftil-alquilo de 1 a 7 átomos de carbono, o halo-alquilo de 1 a 7 átomos de carbono; y opcionalmente uno o más, por ejemplo hasta dos sustituyentes adicionales seleccionados a partir de los otros sustituyentes mencionados para arilo sustituido; en donde el arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido y cicloalquilo mono- o bi-cíclico insustituido o sustituido son de preferencia como se definen anteriormente siempre que se mencionen como parte de acilo, mientras que alquilo insustituido o sustituido es de preferencia como se define más adelante;

alquilo insustituido o sustituido es alquilo de 1 a 20 átomos de carbono, más preferiblemente alquilo de 1 a 7 átomos de carbono, es decir, de cadena recta o ramificada (una o, donde sea apropiado, más veces), el cual está insustituido o sustituido por

una o más, por ejemplo hasta tres fracciones seleccionadas a partir de heterociclilo mono- o bi-cíclico insustituido o sustituido como se describe más adelante, en especial pirrolilo, furanilo, tienilo, tiazolilo, pirazolilo, triazolilo, tetrazolilo, oxetidinilo, 3-(alquilo de 1 a 7 átomos de carbono)-oxetidinilo, piridilo, pirimidinilo, morfolino, tiomorfolino, piperidinilo, piperazinilo, pirrolidinilo, tetrahidrofuran-onilo, tetrahidro-piranilo, 1H-indazanilo, benzo-furanilo, benzo-tiofenilo, isoquinolinilo, quinolinilo o en especial indolilo, cada uno de los cuales está insustituido o sustituido como se describe anteriormente para hetero-ciclilo insustituido o sustituido, por ejemplo por uno a tres sustituyentes independientemente seleccionados a partir de halógeno, hidroxi, alquilo de 1 a 7 átomos de carbono, y alcanoílo de 1 a 7 átomos de carbono; a partir de cicloalquilo mono- o bi-cíclico insustituido o sustituido como se describe anteriormente, en especial ciclopropilo, ciclobutilo, ciclo-pentilo, o ciclohexilo, cada uno de los cuales está insustituido o sustituido como se describe más adelante para cicloalquilo insustituido o sustituido; o en especial a partir del grupo que consiste en alquenilo de 2 a 7 átomos de carbono, alquinilo de 2 a 7 átomos de carbono, halógeno, hidroxi, alcoxilo de 1 a 7 átomos de carbono, halo-alcoxilo de 1 a 7 átomos de carbono, tal como trifluoro-metoxilo, hidroxi-alcoxilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono, fenil- o naftil-oxilo, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono,

alcanoiloxilo de 1 a 7 átomos de carbono, (alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, fenil y/o fenil-alquilo de 1 a 7 átomos de carbono)-amino-carboniloxilo, benzoil- o naftoil-oxilo, tioalquilo de 1 a 7 átomos de carbono, halo-tioalquilo de 1 a 7 átomos de carbono, hidroxi-tioalquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-tioalquilo de 1 a 7 átomos de carbono, tiofenilo o tionaftilo, fenil- o naftil-tioalquilo de 1 a 7 átomos de carbono, nitro, amino, mono- o di-(alquilo de 1 a 7 átomos de carbono, fenilo, naftilo, fenil-alquilo de 1 a 7 átomos de carbono, naftil-alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, y/o alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono)-amino, alcanoílo de 1 a 7 átomos de carbono-amino, benzoil- o naftoil-amino, alquilo de 1 a 7 átomos de carbono-sulfonil-amino, fenil- o naftil-sulfonil-amino, fenil- o naftil-alquilo de 1 a 7 átomos de carbono-sulfonil-amino, fracciones de alquilo de 1 a 7 átomos de carbono, fenil- o naftil-alquilo de 1 a 7 átomos de carbono-carbonil-amino, carboxilo, alquilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, fenil- o naftil-oxicarbonilo, fenil- o naftil-alcoxilo de 1 a 7 átomos de carbono-carbonilo, carbamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, N-mono- o N,N-di-(naftil- o fenil-alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, ciano, sulfenilo, sulfonilo, alquilo de 1 a 7 átomos de carbono-sulfinilo,

fracciones de fenil- o naftil-sulfinilo, fenil- o naftil-alquilo de 1 a 7 átomos de carbono-sulfinilo, sulfonilo, alquilo de 1 a 7 átomos de carbono-sulfonilo, fenil- o naftil-sulfonilo, fenil- o naftil-alquilo de 1 a 7 átomos de carbono-sulfonilo, sulfamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, fenil, naftil, fenil-alquilo de 1 a 7 átomos de carbono, o naftil-alquilo de 1 a 7 átomos de carbono)-amino-sulfonilo, N-mono-, N'-mono-, N,N-di-, o N,N,N'-tri-(alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, fenil y/o fenil-alquilo de 1 a 7 átomos de carbono)-amino-carbonil-amino o -amino-carboniloxilo, y N-mono-, N'-mono-, N,N-di-, o N,N,N'-tri-(alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, y/o alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono)-amino-sulfonil-amino;

en donde cualquier fenilo o naftilo mencionado como sustituyente de, o como parte de un sustituyente de arilo sustituido, está insustituido o sustituido por una o más, de preferencia hasta tres fracciones independientemente seleccionadas a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono, alquenilo de 1 a 7 átomos de carbono, alquinilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, tal como trifluoro-metilo, halógeno, en especial flúor, cloro, bromo o yodo, hidroxi, alcoxilo de 1 a 7 átomos de carbono, feniloxilo, naftiloxilo, fenil- o naftil-alcoxilo de 1 a 7 átomos de

carbono, alcanoiloxilo de 1 a 7 átomos de carbono, fenil- o naftil-alcanoiloxilo de 1 a 7 átomos de carbono, amino, mono- o di-(alquilo de 1 a 7 átomos de carbono, fenil, naftil, fenil-alquilo de 1 a 7 átomos de carbono, naftil-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono, y/o fenil- o naftil-alcanoílo de 1 a 7 átomos de carbono)-amino, carboxilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, fenoxi-carbonilo, naftiloxi-carbonilo, fenil-alquiloxilo de 1 a 7 átomos de carbono-carbonilo, naftil-alcoxilo de 1 a 7 átomos de carbono-carbonilo, carbamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, fenil, naftil, fenil-alquilo de 1 a 7 átomos de carbono, y/o naftil-alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, ciano, sulfo, sulfamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, fenil, naftil, fenil-alquilo de 1 a 7 átomos de carbono, y/o naftil-alquilo de 1 a 7 átomos de carbono)-amino-sulfonilo, y nitro, o de preferencia, en donde se mencionan los sustituyentes preferidos, por uno o más de estos sustituyentes mencionados;

alquenilo insustituido o sustituido es de preferencia alquenilo de 2 a 20 átomos de carbono, más preferiblemente alquenilo de 2 a 7 átomos de carbono con uno o, si es posible, más dobles enlaces, que es de cadena recta o ramificada una o, donde sea apropiado, más veces, el cual está insustituido o sustituido por una o más, por ejemplo hasta tres fracciones seleccionadas a partir de aquéllas mencionadas como sustituyentes para alquilo sustituido, y a partir de arilo mono- o bi-

cíclico insustituido o sustituido, cada uno como se describe anteriormente;

alquinilo insustituido o sustituido es de preferencia alquinilo de 2 a 20 átomos de carbono, más preferiblemente alquinilo de 2 a 7 átomos de carbono con uno o, si es posible, más triples enlaces, que es de cadena recta o ramificada una o, donde sea apropiado, más veces, el cual está insustituido o sustituido por una o más, por ejemplo hasta tres fracciones seleccionadas a partir de aquéllas mencionadas como sustituyentes para alquilo sustituido, y a partir de arilo mono- o bi-cíclico insustituido o sustituido;

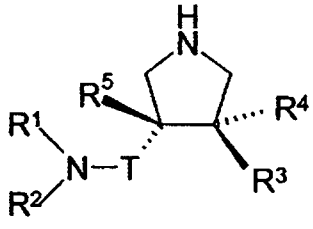
hidroxi esterificado es de preferencia aciloxilo, con acilo como se define en lo anterior, más preferiblemente alcanoiloxilo de 1 a 7 átomos de carbono o benzoiloxilo;

hidroxi eterificado es alquiloxilo de 1 a 7 átomos de carbono insustituido, o de preferencia sustituido, en donde el alquilo sustituido es de preferencia como se define anteriormente, ariloxilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, heterocicliloxilo mono- o bi-cíclico insustituido o sustituido, heterocicliloxilo mono- o bi-cíclico-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, cicloalquiloxilo mono- o bi-cíclico insustituido o sustituido, o cicloalquilo mono- o bi-cíclico-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, en donde, en cada caso, las fracciones de preferencia son como se definen anteriormente, o más preferiblemente

alquiloxilo insustituido, en especial alquiloxilo de 1 a 7 átomos de carbono; y

el anillo de 3 a 7 miembros que contiene nitrógeno formado por R_b y R_c, el cual puede estar insustituido o sustituido, es un anillo de hidrocarburo completamente saturado, parcialmente saturado, o aromático, de preferencia un anillo de hidrocarburo saturado, y está de preferencia insustituido o sustituido por uno o más, por ejemplo por uno a cuatro sustituyentes preferiblemente seleccionados independientemente a partir de aquéllos mencionados en lo anterior como sustituyentes para arilo, en especial un anillo de 4 a 7 miembros que está insustituido o sustituido por hasta cuatro sustituyentes, tal como un sustituyente, seleccionado a partir de hidroxi, halógeno tal como cloro, alquilo de 1 a 7 átomos de carbono tal como metilo, ciano, hidroxi-alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono tal como acetilo, alcoxilo de 1 a 7 átomos de carbono, halo-alcoxilo de 1 a 7 átomos de carbono tal como trifluoro-metoxilo, hidroxi-alcoxilo de 1 a 7 átomos de carbono, y alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono; de preferencia, R_b y R_c forman un anillo de pirrolidina o de piperidina que está sustituido por hasta cuatro fracciones seleccionadas a partir de alquilo de 1 a 7 átomos de carbono, hidroxi, halógeno, hidroxi-alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, y ciano, o de preferencia está insustituido.

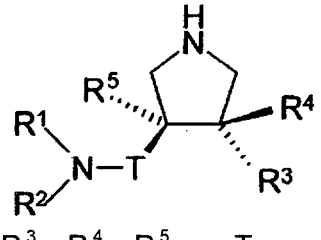
8. El uso de acuerdo con cualquiera de las reivindicaciones 1 a 3 ó 7, el compuesto de la Fórmula I o una sal farmacéuticamente aceptable del mismo para utilizarse de acuerdo con la reivindicación 4 ó 7, o el compuesto de la Fórmula I o una sal del mismo de acuerdo con cualquiera de las reivindicaciones 5 a 7, en donde la Fórmula I tiene la configuración dada en la Fórmula IA:



(IA);

en donde R^1, R^2, R^3, R^4, R^5, y T son como se describen en cualquiera de las reivindicaciones referenciadas.

9. El uso de acuerdo con cualquiera de las reivindicaciones 1 a 3 ó 7, el compuesto de la Fórmula I o una sal farmacéuticamente aceptable del mismo para utilizarse de acuerdo con la reivindicación 4 ó 7, o el compuesto de la Fórmula I o una sal del mismo de acuerdo con cualquiera de las reivindicaciones 5 a 7, en donde la Fórmula I tiene la configuración dada en la Fórmula IB:



(IB);

en donde R^1, R^2, R^3, R^4, R^5, y T son como se describen en

cualquiera de las reivindicaciones referenciadas.

10. El uso de acuerdo con la reivindicación 1, de un compuesto de la Fórmula I, en donde:

R^1 es fenilo, naftilo, heterociclilo mono- o bi-cíclico, fenil-carbonilo, fenil-acetilo, naftil-carbonilo, naftil-acetilo, heterociclilo mono- o bi-cíclico-carbonilo, o acetilo, fenil-sulfonilo, naftil-sulfonilo, o heterociclilo mono- o bi-cíclico-sulfonilo; en donde el heterociclilo mono- o bi-cíclico es pirrolilo, furanilo, tienilo, tiazolilo, pirazolilo, triazolilo, tetrazolilo, oxetidinilo, 3-(alquilo de 1 a 7 átomos de carbono)-oxetidinilo, piridilo, pirimidinilo, morfolino, tio-morfolino, piperidinilo, piperazinilo, pirrolidinilo, tetrahidro-furanilo, tetrahidro-furan-onilo, tetrahidro-piranilo, 1H-indazolilo, benzo-furanilo, benzo-tiofenilo, o de una manera más preferible, isoquinolilo, quinolilo, o en especial indolilo o -2,3-dihidro-benzo-[1,4]-dioxina, y cada heterociclilo mono- o bi-cíclico, fenilo, o naftilo mencionado, está insustituido o de preferencia sustituido por una o más, en especial por una a tres fracciones, de preferencia independientemente seleccionadas a partir del grupo que consiste en:

(i) un sustituyente de la Fórmula -(alquileno de 0 a 7 átomos de carbono)-$(X)_r$-(alquileno de 1 a 7 átomos de carbono)-$(Y)_s$-(alquileno de 0 a 7 átomos de carbono)-H, en donde alquileno de 0 átomos de carbono significa que está presente un enlace en lugar de alquileno enlazado, y alquileno en cada caso puede ser de cadena recta o ramificada, y puede estar insustituido o

sustituido, por ejemplo, por una o más fracciones como se definen para alquilo sustituido, en especial por halógeno, especialmente flúor, hidroxi, alcoxilo de 1 a 7 átomos de carbono, feniloxilo, naftiloxilo, alcanoiloxilo de 1 a 7 átomos de carbono, benzoiloxilo, naftoiloxilo, amino, mono- o di-(alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono, fenil-alcanoílo de 1 a 7 átomos de carbono, naftil-alcanoílo de 1 a 7 átomos de carbono, fenilo, naftilo, fenil-alquilo de 1 a 7 átomos de carbono, y/o naftil-alquilo de 1 a 7 átomos de carbono)-amino, carboxilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, o ciano; **r** y **s**, cada uno independiente-mente del otro, son 0 ó 1, y cada uno de X e Y, si están presentes e independientemente de los otros, es -O-, -NV-, -S-, -O-CO-, -CO-O-, -NV-CO-; -CO-NV-; -NV-SO_2-; -SO_2-NV; -NV-CO-NV-, -NV-CO-O-, -O-CO-NV-, -NV-SO_2-NV-, en donde V es hidrógeno o alquilo insustituido o sustituido como se define más adelante, en especial alquilo de 1 a 7 átomos de carbono, o es fenilo, naftilo, fenil- o naftil-alquilo de 1 a 7 átomos de carbono, o halo-alquilo de 1 a 7 átomos de carbono; por ejemplo, alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, feniloxi- o naftiloxi-alquilo de 1 a 7 átomos de carbono, alcanoiloxilo de 1 a 7 átomos de carbono- alquilo de 1 a 7 átomos de carbono, amino-alquilo de 1 a

7 átomos de carbono, tal como amino-metilo, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-amino-alquilo de 1 a 7 átomos de carbono, mono- o di- (alquilo de 1 a 7 átomos de carbono, naftil, fenil, naftil-alquilo de 1 a 7 átomos de carbono, y/o fenil-alquilo de 1 a 7 átomos de carbono)-amino-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono-amino-alquilo de 1 a 7 átomos de carbono, alquilo de 1 a 7 átomos de carbono-O-CO-NH-alquilo de 1 a 7 átomos de carbono, alquilo de 1 a 7 átomos de carbono-sulfonil-amino-alquilo de 1 a 7 átomos de carbono, alquilo de 1 a 7 átomos de carbono-NH-CO-NH-alquilo de 1 a 7 átomos de carbono, alquilo de 1 a 7 átomos de carbono-NH-SO_2-NH-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono, hidroxi-alcoxilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono, alcanoiloxilo de 1 a 7 átomos de carbono, halo-alcoxilo de 1 a 7 átomos de carbono, tal como fluoro-metoxilo, fenil- o naftil-alcanoiloxilo de 1 a 7 átomos de carbono, fenil- o naftil-alquilo de 1 a 7 átomos de carbono-amino-carboniloxilo, halo-tioalquilo de 1 a 7 átomos de carbono, fenil- o naftil-tioalquilo de 1 a 7 átomos de carbono, mono- o di-(alquilo de 1 a 7 átomos de carbono-, naftil-alquilo de 1 a 7 átomos de carbono-, fenil-alquilo de 1 a 7 átomos de carbono-, y/o alcoxilo de 1 a 7 átomos de carbono-alquilo (de 1 a 7 átomos de carbono)-amino, alcanoílo de 1 a 7 átomos de carbono-amino, alquilo de 1 a 7 átomos de carbono-sulfonil-amino, fenil- o naftil-alcanoílo de 1 a

7 átomos de carbono-amino, fenil- o naftil-alquilo de 1 a 7 átomos de carbono-amino-carbonil-amino, carboxi-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-carbonilo, hidroxi-alcoxilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono-carbonilo, amino-alcoxilo de 1 a 7 átomos de carbono-carbonilo, (N-) mono-(alquilo de 1 a 7 átomos de carbono)-amino-alcoxilo de 1 a 7 átomos de carbono-carbonilo, alcanoílo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono-carbonilo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, naftil-alquilo de 1 a 7 átomos de carbono, y/o fenil-alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, alquilo de 1 a 7 átomos de carbono-sulfonilo, halo-alquilo de 1 a 7 átomos de carbono-sulfonilo, hidroxi-alquilo de 1 a 7 átomos de carbono-sulfonilo, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-sulfonilo, amino-alquilo de 1 a 7 átomos de carbono-sulfonilo, N-mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino-alquilo de 1 a 7 átomos de carbono-sulfonilo, alcanoílo de 1 a 7 átomos de carbono-amino-alquilo de 1 a 7 átomos de carbono-sulfonilo, N-alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-carbamoílo, o N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino-sulfonilo;

(ii) a partir de alquenilo de 2 a 7 átomos de carbono, alquinilo de 2 a 7 átomos de carbono, fenilo, naftilo, hetero-ciclilo mono- o bi-cíclico, en especial como se define más adelante para

heterociclilo mono- o bi-cíclico, de preferencia seleccionado a partir de pirrolilo, furanilo, tienilo, pirimidin-2,4-dion-1-, -3-, ó -5-ilo. tetrahidro-piranilo y tetrahidro-furanilo, fenil- o naftil-, o (heterociclilo mono- o bi-cíclico)-alquilo de 1 a 7 átomos de carbono o alquiloxilo de 1 a 7 átomos de carbono, en donde heterociclilo mono- o bi-cíclico es como se define más adelante, de preferencia seleccionado a partir de pirrolilo, furanilo, tetrahidrofuranilo, tetrahidropiranilo, y tienilo; tetrahidro-furanil- o tetrahidro-piranil-alquiloxilo de 1 a 7 átomos de carbono-carbonilo, benzoil- o naftoil-amino-alquilo de 1 a 7 átomos de carbono, (fenil- o naftil- o heterociclilo mono- o bi-cíclico)-sulfonil-amino-alquilo de 1 a 7 átomos de carbono, en donde fenilo o naftilo o heterociclilo mono- o bi-cíclico está insustituido o sustituido, de preferencia por una o más, en especial por una a tres fracciones de alquilo de 1 a 7 átomos de carbono, (fenil o naftil o heterociclilo mono- o bi-cíclico)-alquilo de 1 a 7 átomos de carbono-sulfonil-amino-alquilo de 1 a 7 átomos de carbono, halógeno, hidroxi, fenil-alcoxilo de 1 a 7 átomos de carbono en donde el fenilo está de preferencia insustituido o sustituido, de preferencia por alcoxilo de 1 a 7 átomos de carbono y/o halógeno, heterociclilo mono- o bi-cíclico-alcoxilo de 1 a 7 átomos de carbono, (heterociclilo mono- o bi-cíclico o fenil o naftil)-oxilo, naftil-alquiloxilo de 1 a 7 átomos de carbono, (benzoil o naftoil o heterociclilo mono- o bi-cíclico-carbonil)-oxilo, (fenil o naftil o hetero-ciclilo mono- o bi-cíclico)-amino-carboniloxilo, (fenil o naftil

o heterociclilo mono- o bi-cíclico)-tio, (benzoil o naftoil o heterociclilo mono- o bi-cíclico)-tio, nitro, amino, di-((naftil o fenil o heterociclilo mono- o bi-cíclico)-alquilo de 1 a 7 átomos de carbono)-amino, (benzoil o naftoil o heterociclilo mono- o bi-cíclico)-amino, (fenil o naftil o heterociclilo mono- o bi-cíclico)-sulfonil-amino, en donde el fenilo o naftilo está insustituido o sustituido, de preferencia por una o más, en especial por una a tres fracciones de alquilo de 1 a 7 átomos de carbono, (fenil o naftil o heterociclilo mono- o bi-cíclico)-alquilo de 1 a 7 átomos de carbono-sulfonil-amino, (fenil o naftil o heterociclilo mono- o bi-cíclico)-amino-carbonil-amino, (fenil o naftil o heterociclilo mono- o bi-cíclico)-oxicarbonil-amino, (fenil o naftil o heterociclilo mono- o bi-cíclico)-alquiloxilo de 1 a 7 átomos de carbono-carbonil-amino, carboxilo, alquilo de 1 a 7 átomos de carbono-carbonilo, halo-alquilo de 1 a 7 átomos de carbono-carbonilo, hidroxi-alquilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-carbonilo, amino-alquilo de 1 a 7 átomos de carbono-carbonilo, (N-) mono- o (N,N-) di-(alquilo de 1 a 7 átomos de carbono)-amino-alquilo de 1 a 7 átomos de carbono-carbonilo, alcanoílo de 1 a 7 átomos de carbono-amino-alquilo de 1 a 7 átomos de carbono-carbonilo, halo-alcoxilo de 1 a 7 átomos de carbono-carbonilo, (fenil o naftil o heterociclilo mono- o bi-cíclico)-oxi-carbonilo, (fenil o naftil o heterociclilo mono- o bi-cíclico)-alcoxilo de 1 a 7 átomos de carbono-carbonilo, (N,N-) di-(alquilo de 1 a 7 átomos de carbono)-

amino-alcoxilo de 1 a 7 átomos de carbono-carbonilo, carbamoílo, N-mono- o N,N-di-(naftil o fenil o heterociclilo mono- o bi-cíclico)-amino-carbonilo, ciano, alquileno de 1 a 7 átomos de carbono que está insustituido o sustituido por hasta cuatro sustituyentes de alquilo de 1 a 7 átomos de carbono, y enlazado a dos átomos adyacentes del anillo de la fracción de arilo, sulfenilo, sulfinilo, alquilo de 1 a 7 átomos de carbono-sulfinilo, (fenil o naftil o heterociclilo mono- o bi-cíclico)-sulfinilo en donde el fenilo o naftilo está insustituido o sustituido de preferencia por una o más, en especial por una a tres fracciones de alquilo de 1 a 7 átomos de carbono, fenil- o naftil-alquilo de 1 a 7 átomos de carbono-sulfinilo, sulfonilo, (fenil o naftil o heterociclilo mono- o bi-cíclico)-sulfonilo en donde el fenilo o naftilo está insustituido o sustituido de preferencia por una o más, en especial por una a tres fracciones de alquilo de 1 a 7 átomos de carbono, (fenil o naftil o heterociclilo mono- o bi-cíclico)-alquilo de 1 a 7 átomos de carbono-sulfonilo, sulfamoílo, y N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, fenil, naftil, heterociclilo mono- o bi-cíclico, fenil-alquilo de 1 a 7 átomos de carbono, naftil-alquilo de 1 a 7 átomos de carbono, y/o heterociclilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono)-amino-sulfonilo;

en donde cualquier fenilo o naftilo o heterociclilo mono- o bi-cíclico - cuyo heterociclilo mono- o bi-cíclico de preferencia es como se define para heterociclilo mono- o bi-cíclico, más preferiblemente se selecciona a partir de pirrolilo, furanilo,

tetrahidrofuranilo, tetrahidropiranilo, y tienilo - mencionado como sustituyente de, o como parte de un sustituyente de heterociclilo mono- o bi-cíclico, fenilo o naftilo R^1 bajo (i) ó (ii) está insustituido o sustituido por una o más, de preferencia hasta tres fracciones independientemente seleccionadas a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono, alquenilo de 1 a 7 átomos de carbono, alquinilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, halógeno, hidroxi, alcoxilo de 1 a 7 átomos de carbono, feniloxilo, naftiloxilo, fenil- o naftil-alcoxilo de 1 a 7 átomos de carbono, alcanoiloxilo de 1 a 7 átomos de carbono, fenil- o naftil-alcanoiloxilo de 1 a 7 átomos de carbono, amino, mono- o di-(alquilo de 1 a 7 átomos de carbono, fenil, naftil, fenil-alquilo de 1 a 7 átomos de carbono, naftil-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono, y/o fenil- o naftil-alcanoílo de 1 a 7 átomos de carbono)-amino, carboxilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, fenoxi-carbonilo, naftiloxi-carbonilo, fenil-alquiloxilo de 1 a 7 átomos de carbono-carbonilo, naftil-alcoxilo de 1 a 7 átomos de carbono-carbonilo, carbamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, fenil, naftil, fenil-alquilo de 1 a 7 átomos de carbono, y/o naftil-alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, ciano, sulfo, sulfamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, fenil, naftil, fenil-alquilo de 1 a 7 átomos de carbono, y/o naftil-alquilo de 1 a 7 átomos de carbono)-amino-sulfonilo, y nitro, o de preferencia, en donde se mencionan los sustituyentes

preferidos, por uno o más de estos sustituyentes mencionados;

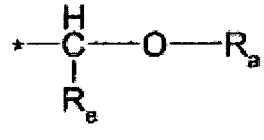
R^2 es fenilo, naftilo, fenil-alquilo de 1 a 7 átomos de carbono, o naftil-alquilo de 1 a 7 átomos de carbono, en donde cada fenilo o naftilo mencionados hasta ahora en la definición de R^2 está insustituido o sustituido como justamente se describió para fenilo o naftilo sustituido en la definición de R^1, o es de preferencia cicloalquilo de 3 a 8 átomos de carbono, o es alquilo de 1 a 7 átomos de carbono que está insustituido o sustituido por uno o más, en especial hasta tres, por ejemplo uno o dos sustituyentes independientemente seleccionados a partir del grupo que consiste en alquenilo de 2 a 7 átomos de carbono, alquinilo de 2 a 7 átomos de carbono, halógeno, hidroxi, alcoxilo de 1 a 7 átomos de carbono, halo-alcoxilo de 1 a 7 átomos de carbono, hidroxi-alcoxilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono, fenil- o naftil-oxilo, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono, alcanoiloxilo de 1 a 7 átomos de carbono, (alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, fenilo, y/o fenil-alquilo de 1 a 7 átomos de carbono)-amino-carboniloxilo, benzoil- o naftoil-oxilo, tioalquilo de 1 a 7 átomos de carbono, halo-tioalquilo de 1 a 7 átomos de carbono, tal como trifluoro-tiometilo, hidroxi-tioalquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-tioalquilo de 1 a 7 átomos de carbono, tiofenilo o tionaftilo, fenil- o naftil-tioalquilo de 1 a 7

átomos de carbono, nitro, amino, mono- o di-(alquilo de 1 a 7 átomos de carbono, fenilo, naftilo, fenil-alquilo de 1 a 7 átomos de carbono, naftil-alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, y/o alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono)-amino, alcanoílo de 1 a 7 átomos de carbono-amino, benzoil- o naftoil-amino, fenil- o naftil-alquilo de 1 a 7 átomos de carbono-carbonil-amino, alquilo de 1 a 7 átomos de carbono-sulfonil-amino, fenil- o naftil-sulfonil-amino, en donde el fenilo o naftilo está insustituido o sustituido por una o más, en especial por una a tres fracciones de alquilo de 1 a 7 átomos de carbono, fenil- o naftil-alquilo de 1 a 7 átomos de carbono-sulfonil-amino, carboxilo, alquilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, fenil- o naftil-oxicarbonilo, fenil- o naftil-alcoxilo de 1 a 7 átomos de carbono-carbonilo, carbamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, N-mono- o N,N-di-(naftil- o fenil-alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, ciano, sulfenilo, sulfonilo, alquilo de 1 a 7 átomos de carbono-sulfinilo, fenil- o naftil-sulfinilo, en donde fenilo o naftilo está insustituido o sustituido por una o más, en especial por una a tres fracciones de alquilo de 1 a 7 átomos de carbono, fenil- o naftil-alquilo de 1 a 7 átomos de carbono-sulfinilo, sulfonilo, alquilo de 1 a 7 átomos de carbono-sulfonilo, fenil- o naftil-sulfonilo, en donde el fenilo o naftilo está insustituido o sustituido por una o más, en especial por una a tres fracciones de alquilo de 1 a 7 átomos de carbono, fenil-

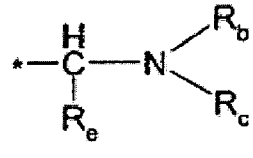
o naftil-alquilo de 1 a 7 átomos de carbono-sulfonilo, sulfamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, fenilo, naftilo, fenil-alquilo de 1 a 7 átomos de carbono, o naftil-alquilo de 1 a 7 átomos de carbono)-amino-sulfonilo, N-mono-, N'-mono-, N,N-di-, ó N,N,N'-tri-(alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, fenilo, y/o fenil-alquilo de 1 a 7 átomos de carbono)-amino-carbonil-amino o -amino-carboniloxilo, y N-mono-, N'-mono-, N,N-di-, ó N,N,N'-tri-(alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, y/o alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono)-amino-sulfonil-amino; o es cicloalquilo de 3 a 10 átomos de carbono, o ciclo-alquilo de 3 a 10 átomos de carbono-alquilo de 1 a 7 átomos de carbono;

R^3 es una fracción seleccionada a partir del grupo de fracciones de las fórmulas:

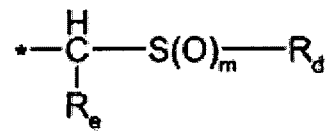
(a)



(b)

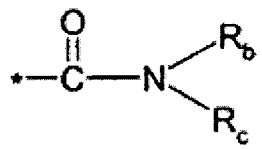


(c)



y

(f)



en donde, en cualquiera de las fracciones de las fórmulas dadas anteriormente bajo (a), (b), (c), y (f), el asterisco (*) muestra el enlace que enlaza a la fracción R^3 respectiva con el resto de la molécula en la Fórmula I;

R_a es acilo seleccionado a partir de alcanoílo de 1 a 7 átomos de carbono, fenil-alcanoílo de 1 a 7 átomos de carbono insustituido o mono-, di-, o tri-sustituido por (halo-alcoxilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono-alquiloxilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, y/o alquilo de 1 a 7 átomos de carbono), cicloalquilo de 3 a 8 átomos de carbono-carbonilo, o cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono-carbonilo, (tetrahidro-furanil o tetrahidro-piranil)-carbonilo, o (tetrahidrofuranil o tetrahidropiranil)-alquilo de 1 a 7 átomos de carbono-carbonilo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, N-[fenil, o fenil-alquilo de 1 a 7 átomos de carbono]-amino-carbonilo, N-[cicloalquilo de 3 a 8

átomos de carbono o cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono]-amino-carbonilo, alquilo de 1 a 7 átomos de carbono-amino-carbonilo, N-(fenil-alquilo de 1 a 7 átomos de carbono)-(alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, N-(fenil-alquilo de 1 a 7 átomos de carbono)-(cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, N-(alquilo de 1 a 7 átomos de carbono)-(cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, N-(fenil-alquilo de 1 a 7 átomos de carbono)-(cicloalquilo de 3 a 8 átomos de carbono)-amino-carbonilo, N-(heterociclil-alquilo de 1 a 7 átomos de carbono)-(cicloalquilo de 3 a 8 átomos de carbono)-amino-carbonilo, N-(heterociclil)-(ciclo-alquilo de 3 a 8 átomos de carbono)-amino-carbonilo; o es hidrógeno;

R_b es alquilo de 1 a 7 átomos de carbono o fenilo, naftilo, fenil-alquilo de 1 a 7 átomos de carbono, o naftil-alquilo de 1 a 7 átomos de carbono - en cada caso insustituido o sustituido -, en donde, en el caso de una fracción sustituida, los sustituyentes son uno o más, en especial hasta tres sustituyentes independientemente seleccionados a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono, alquenilo de 2 a 7 átomos de carbono, alquinilo de 2 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, tal como trifluoro-metilo, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, amino-alquilo de 1 a

7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono, hidroxi-alcoxilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono, alcanoiloxilo de 1 a 7 átomos de carbono, amino, mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino, alcanoílo de 1 a 7 átomos de carbono-amino, alquilo de 1 a 7 átomos de carbono-sulfonil-amino, alcoxilo de 1 a 7 átomos de carbono-carbonilo, carboxi-alquilo de 1 a 7 átomos de carbono, halógeno, hidroxi, halo-alcoxilo de 1 a 7 átomos de carbono, halo-tioalquilo de 1 a 7 átomos de carbono, nitro, carboxilo, alquilo de 1 a 7 átomos de carbono-carbonilo, halo-alquilo de 1 a 7 átomos de carbono-carbonilo, hidroxi-alquilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-carbonilo, halo-alcoxilo de 1 a 7 átomos de carbono-carbonilo, carbamoílo, ciano, alquilo de 1 a 7 átomos de carbono-sulfinilo, sulfonilo, alquilo de 1 a 7 átomos de carbono-sulfonilo, halo-alquilo de 1 a 7 átomos de carbono-sulfonilo, hidroxi-alquilo de 1 a 7 átomos de carbono-sulfonilo, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-sulfonilo, sulfamoílo, y N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino-sulfonilo; o es acilo, por ejemplo como justamente se definió bajo R_a, en particular alcanoílo de 1 a 7 átomos de carbono, fenil-alcanoílo de 1 a 7 átomos de carbono insustituido o mono-, di-, o tri-sustituido por (halógeno, alcoxilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono-alquiloxilo de 1 a 7 átomos de carbono,

alquiloxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, y/o alquilo de 1 a 7 átomos de carbono), cicloalquilo de 3 a 8 átomos de carbono-carbonilo, o cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono-carbonilo, (tetrahidrofuranil o tetrahidropiranil)-carbonilo o (tetrahidro-furanil o tetrahidropiranil)-alquilo de 1 a 7 átomos de carbono-carbonilo, (fenil- o fenil-alquilo de 1 a 7 átomos de carbono)-sulfonilo insustituido o mono-, di-, o tri-sustituido por (halógeno y/o alquilo de 1 a 7 átomos de carbono), alquilo de 1 a 7 átomos de carbono-sulfonilo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, N-[cicloalquilo de 3 a 8 átomos de carbono o cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono]-amino-carbonilo, alquilo de 1 a 7 átomos de carbono-amino-carbonilo, N-(fenil-alquilo de 1 a 7 átomos de carbono)-(alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, N-(fenil-alquilo de 1 a 7 átomos de carbono)-(cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, N-(alquilo de 1 a 7 átomos de carbono)-(cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, N-(fenil-alquilo de 1 a 7 átomos de carbono)-(cicloalquilo de 3 a 8 átomos de carbono)-amino-carbonilo, N-(heterociclil-alquilo de 1 a 7 átomos de carbono)-(cicloalquilo de 3 a 8 átomos de carbono)-amino-carbonilo, N-(heterociclil)-(cicloalquilo de 3 a 8 átomos de carbono)-amino-carbonilo, o (alquilo de 1 a 7 átomos de carbono, fenilo, naftilo, fenil-alquilo de

1 a 7 átomos de carbono, naftil-alquilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, ciclo-alquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono, heterociclilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono, y/o heterociclilo mono- o bi-cíclico seleccionado de preferencia a partir de pirrolilo, furanilo, tienilo (= tiofenilo), tiazolilo, pirazolilo, triazolilo, tetrazolilo, oxetidinilo, 3-(alquilo de 1 a 7 átomos de carbono)-oxetidinilo, piridilo, pirimidinilo, morfolino, tio-morfolino, piperidinilo, piperazinilo, pirrolidinilo, 1H-indazanilo, benzofuranilo, benzotiofenilo, (más preferible-mente) isoquinolinilo, quinolinilo, tetrahidrofuran-onilo, tetrahidro-piranilo, indolil)-oxicarbonilo, y (tetrahidrofuranil o tetrahidropiranil)-alquiloxilo de 1 a 7 átomos de carbono-carbonilo, o se selecciona a partir de (fenil- o fenil-alquilo de 1 a 7 átomos de carbono)-sulfonilo insustituido o mono-, di-, o tri-sustituido por (halógeno y/o alquilo de 1 a 7 átomos de carbono), alquilo de 1 a 7 átomos de carbono-sulfonilo;

R_c es hidroxi-alquilo de 1 a 7 átomos de carbono, o alquiloxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono, o de preferencia ciclo-alquilo de 3 a 8 átomos de carbono, hidrógeno, o alquilo de 1 a 7 átomos de carbono;

R_d es fenil- o naftil-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, en donde, en el caso de una fracción sustituida, los sustituyentes son uno o más, en especial hasta tres

sustituyentes independientemente seleccionados a partir de aquéllos mencionados para fenil- o naftil-alquilo de 1 a 7 átomos de carbono insustituido o sustituido bajo R_b, o es $-N(R_b)(R_c)$;

R_e es alquilo de 1 a 7 átomos de carbono, o de preferencia hidrógeno; y

m es 2;

cada uno de R^4 y R^5 se selecciona, independiente-mente uno del otro, a partir de alquilo de 1 a 7 átomos de carbono, hidroxi, alquiloxilo de 1 a 7 átomos de carbono, o de preferencia hidrógeno;

y T es carbonilo, o de preferencia metileno;

o una sal farmacéuticamente aceptable del mismo, para la fabricación de una formulación farmacéutica para el tratamiento de una enfermedad que dependa de la actividad de la renina, en especial hipertensión.

11. Un compuesto de la Fórmula I de acuerdo con la reivindicación 5, en donde:

R^1 es fenilo, naftilo, heterociclilo mono- o bi-cíclico, fenil-carbonilo, fenil-acetilo, naftil-carbonilo, naftil-acetilo, heterociclilo mono- o bi-cíclico-carbonilo, o acetilo, fenil-sulfonilo, naftil-sulfonilo, o heterociclilo mono- o bi-cíclico-sulfonilo; en donde el heterociclilo mono- o bi-cíclico es pirrolilo, furanilo, tienilo, tiazolilo, pirazolilo, triazolilo, tetrazolilo, oxetidinilo, 3-(alquilo de 1 a 7 átomos de carbono)-oxetidinilo, piridilo, pirimidinilo,

morfolino, tio-morfolino, piperidinilo, piperazinilo, pirrolidinilo, tetrahidro-furanilo, tetrahidro-furan-onilo, tetrahidro-piranilo, 1H-indazolilo, benzo-furanilo, benzo-tiofenilo, o de una manera más preferible, isoquinolilo, quinolilo, o en especial indolilo o -2,3-dihidro-benzo-[1,4]-dioxina, y cada heterociclilo mono- o bi-cíclico, fenilo, o naftilo mencionado, está insustituido o de preferencia sustituido por una o más, en especial por una a tres fracciones, de preferencia independientemente seleccionadas a partir del grupo que consiste en:

(i) un sustituyente de la Fórmula -(alquileno de 0 a 7 átomos de carbono)-$(X)_r$-(alquileno de 1 a 7 átomos de carbono)-$(Y)_s$-(alquileno de 0 a 7 átomos de carbono)-H (en especial en arilo sustituido o en aril-alquilo sustituido como R^1), en donde alquileno de 0 átomos de carbono significa que está presente un enlace en lugar de alquileno enlazado, y alquileno en cada caso puede ser de cadena recta o ramificada, y puede estar insustituido o sustituido, por ejemplo, por una o más fracciones como se definen para alquilo sustituido, en especial por halógeno, especialmente flúor, hidroxi, alcoxilo de 1 a 7 átomos de carbono, feniloxilo, naftiloxilo, alcanoiloxilo de 1 a 7 átomos de carbono, benzoiloxilo, naftoiloxilo, amino, mono- o di-(alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono, fenil-alcanoílo de 1 a 7 átomos de carbono, naftil-alcanoílo de 1 a 7 átomos de carbono, fenilo, naftilo, fenil-alquilo de 1 a 7 átomos de carbono, y/o naftil-alquilo de 1 a 7 átomos de carbono)-amino, carboxilo,

alcoxilo de 1 a 7 átomos de carbono-carbonilo, o ciano; **r** y **s**, cada uno independiente-mente del otro, son 0 ó 1, y cada uno de X e Y, si están presentes e independientemente de los otros, es -O-, -NV-, -S-, -O-CO-, -CO-O-, -NV-CO-; -CO-NV-; -NV-SO_2-; -SO_2-NV; -NV-CO-NV-, -NV-CO-O-, -O-CO-NV-, -NV-SO_2-NV-, en donde V es hidrógeno o alquilo insustituido o sustituido como se define más adelante, en especial alquilo de 1 a 7 átomos de carbono, o es fenilo, naftilo, fenil- o naftil-alquilo de 1 a 7 átomos de carbono, o halo-alquilo de 1 a 7 átomos de carbono; por ejemplo, alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, feniloxi- o naftiloxi-alquilo de 1 a 7 átomos de carbono, alcanoiloxilo de 1 a 7 átomos de carbono- alquilo de 1 a 7 átomos de carbono, amino-alquilo de 1 a 7 átomos de carbono, tal como amino-metilo, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-amino-alquilo de 1 a 7 átomos de carbono, mono- o di- (alquilo de 1 a 7 átomos de carbono, naftil, fenil, naftil-alquilo de 1 a 7 átomos de carbono, y/o fenil-alquilo de 1 a 7 átomos de carbono)-amino-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono-amino-alquilo de 1 a 7 átomos de carbono, alquilo de 1 a 7 átomos de carbono-O-CO-NH-alquilo de 1 a 7 átomos de carbono, alquilo de 1 a 7 átomos de carbono-sulfonil-amino-alquilo

de 1 a 7 átomos de carbono, alquilo de 1 a 7 átomos de carbono-NH-CO-NH-alquilo de 1 a 7 átomos de carbono, alquilo de 1 a 7 átomos de carbono-NH-SO_2-NH-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono, hidroxi-alcoxilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono, alcanoiloxilo de 1 a 7 átomos de carbono, halo-alcoxilo de 1 a 7 átomos de carbono, tal como fluoro-metoxilo, fenil- o naftil-alcanoiloxilo de 1 a 7 átomos de carbono, fenil- o naftil-alquilo de 1 a 7 átomos de carbono-amino-carboniloxilo, halo-tioalquilo de 1 a 7 átomos de carbono, fenil- o naftil-tioalquilo de 1 a 7 átomos de carbono, mono- o di-(alquilo de 1 a 7 átomos de carbono-, naftil-alquilo de 1 a 7 átomos de carbono-, fenil-alquilo de 1 a 7 átomos de carbono-, y/o alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-)amino, alcanoílo de 1 a 7 átomos de carbono-amino, alquilo de 1 a 7 átomos de carbono-sulfonil-amino, fenil- o naftil-alcanoílo de 1 a 7 átomos de carbono-amino, fenil- o naftil-alquilo de 1 a 7 átomos de carbono-amino-carbonil-amino, carboxi-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-carbonilo, hidroxi-alcoxilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono-carbonilo, amino-alcoxilo de 1 a 7 átomos de carbono-carbonilo, (N-) mono-(alquilo de 1 a 7 átomos de carbono)-amino-alcoxilo de 1 a 7 átomos de carbono-carbonilo, alcanoílo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono-carbonilo, N-mono- o

N,N-di-(alquilo de 1 a 7 átomos de carbono, naftil-alquilo de 1 a 7 átomos de carbono, y/o fenil-alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, alquilo de 1 a 7 átomos de carbono-sulfonilo, halo-alquilo de 1 a 7 átomos de carbono-sulfonilo, hidroxi-alquilo de 1 a 7 átomos de carbono-sulfonilo, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-sulfonilo, amino-alquilo de 1 a 7 átomos de carbono-sulfonilo, N-mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino-alquilo de 1 a 7 átomos de carbono-sulfonilo, alcanoílo de 1 a 7 átomos de carbono-amino-alquilo de 1 a 7 átomos de carbono-sulfonilo, N-alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-carbamoílo, o N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino-sulfonilo;

(ii) a partir de alquenilo de 2 a 7 átomos de carbono, alquinilo de 2 a 7 átomos de carbono, fenilo, naftilo, hetero-ciclilo mono- o bi-cíclico, en especial como se define más adelante para heterociclilo mono- o bi-cíclico, de preferencia seleccionado a partir de pirrolilo, furanilo, tienilo, pirimidin-2,4-dion-1-, -3-, ó -5-ilo. tetrahidro-piranilo y tetrahidro-furanilo, fenil- o naftil-, o (heterociclilo mono- o bi-cíclico)-alquilo de 1 a 7 átomos de carbono o alquiloxilo de 1 a 7 átomos de carbono, en donde heterociclilo mono- o bi-cíclico es como se define más adelante, de preferencia seleccionado a partir de pirrolilo, furanilo, tetrahidrofuranilo, tetrahidropiranilo, y tienilo; tetrahidro-furanil- o tetrahidro-piranil-alquiloxilo de 1 a 7 átomos de carbono-carbonilo,

benzoil- o naftoil-amino-alquilo de 1 a 7 átomos de carbono, (fenil- o naftil- o heterociclilo mono- o bi-cíclico)-sulfonil-amino-alquilo de 1 a 7 átomos de carbono, en donde fenilo o naftilo o heterociclilo mono- o bi-cíclico está insustituido o sustituido, de preferencia por una o más, en especial por una a tres fracciones de alquilo de 1 a 7 átomos de carbono, (fenil o naftil o heterociclilo mono- o bi-cíclico)-alquilo de 1 a 7 átomos de carbono-sulfonil-amino-alquilo de 1 a 7 átomos de carbono, halógeno, hidroxi, fenil-alcoxilo de 1 a 7 átomos de carbono en donde el fenilo está de preferencia insustituido o sustituido, de preferencia por alcoxilo de 1 a 7 átomos de carbono y/o halógeno, heterociclilo mono- o bi-cíclico-alcoxilo de 1 a 7 átomos de carbono, (heterociclilo mono- o bi-cíclico o fenil o naftil)-oxilo, naftil-alquiloxilo de 1 a 7 átomos de carbono, (benzoil o naftoil o heterociclilo mono- o bi-cíclico-carbonil)-oxilo, (fenil o naftil o hetero-ciclilo mono- o bi-cíclico)-amino-carboniloxilo, (fenil o naftil o heterociclilo mono- o bi-cíclico)-tio, (benzoil o naftoil o heterociclilo mono- o bi-cíclico)-tio, nitro, amino, di-((naftil o fenil o heterociclilo mono- o bi-cíclico)-alquilo de 1 a 7 átomos de carbono)-amino, (benzoil o naftoil o heterociclilo mono- o bi-cíclico)-amino, (fenil o naftil o heterociclilo mono- o bi-cíclico)-sulfonil-amino, en donde el fenilo o naftilo está insustituido o sustituido, de preferencia por una o más, en especial por una a tres fracciones de alquilo de 1 a 7 átomos de carbono, (fenil o naftil o heterociclilo mono- o bi-cíclico)-alquilo de 1 a 7 átomos de

carbono-sulfonil-amino, (fenil o naftil o heterociclilo mono- o bi-cíclico)-amino-carbonil-amino, (fenil o naftil o heterociclilo mono- o bi-cíclico)-oxicarbonil-amino, (fenil o naftil o heterociclilo mono- o bi-cíclico)-alquiloxilo de 1 a 7 átomos de carbono-carbonil-amino, carboxilo, alquilo de 1 a 7 átomos de carbono-carbonilo, halo-alquilo de 1 a 7 átomos de carbono-carbonilo, hidroxi-alquilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-carbonilo, amino-alquilo de 1 a 7 átomos de carbono-carbonilo, (N-) mono- o (N,N-) di-(alquilo de 1 a 7 átomos de carbono)-amino-alquilo de 1 a 7 átomos de carbono-carbonilo, alcanoílo de 1 a 7 átomos de carbono-amino-alquilo de 1 a 7 átomos de carbono-carbonilo, halo-alcoxilo de 1 a 7 átomos de carbono-carbonilo, (fenil o naftil o heterociclilo mono- o bi-cíclico)-oxi-carbonilo, (fenil o naftil o heterociclilo mono- o bi-cíclico)-alcoxilo de 1 a 7 átomos de carbono-carbonilo, (N,N-) di-(alquilo de 1 a 7 átomos de carbono)-amino-alcoxilo de 1 a 7 átomos de carbono-carbonilo, carbamoílo, N-mono- o N,N-di-(naftil o fenil o heterociclilo mono- o bi-cíclico)-amino-carbonilo, ciano, alquileno de 1 a 7 átomos de carbono que está insustituido o sustituido por hasta cuatro sustituyentes de alquilo de 1 a 7 átomos de carbono, y enlazado a dos átomos adyacentes del anillo de la fracción de arilo, sulfenilo, sulfinilo, alquilo de 1 a 7 átomos de carbono-sulfinilo, (fenil o naftil o heterociclilo mono- o bi-cíclico)-sulfinilo en donde el fenilo o naftilo está insustituido o sustituido de preferencia por una o más,

en especial por una a tres fracciones de alquilo de 1 a 7 átomos de carbono, fenil- o naftil-alquilo de 1 a 7 átomos de carbono-sulfinilo, sulfonilo, (fenil o naftil o heterociclilo mono- o bi-cíclico)-sulfonilo en donde el fenilo o naftilo está insustituido o sustituido de preferencia por una o más, en especial por una a tres fracciones de alquilo de 1 a 7 átomos de carbono, (fenil o naftil o heterociclilo mono- o bi-cíclico)-alquilo de 1 a 7 átomos de carbono-sulfonilo, sulfamoílo, y N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, fenil, naftil, heterociclilo mono- o bi-cíclico, fenil-alquilo de 1 a 7 átomos de carbono, naftil-alquilo de 1 a 7 átomos de carbono, y/o heterociclilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono)-amino-sulfonilo;

en donde cualquier fenilo o naftilo o heterociclilo mono- o bi-cíclico - cuyo heterociclilo mono- o bi-cíclico de preferencia es como se define para heterociclilo mono- o bi-cíclico, más preferiblemente se selecciona a partir de pirrolilo, furanilo, tetrahidrofuranilo, tetrahidropiranilo, y tienilo - mencionado como sustituyente de, o como parte de un sustituyente de heterociclilo mono- o bi-cíclico, fenilo o naftilo R^1 bajo (i) ó (ii) está insustituido o sustituido por una o más, de preferencia hasta tres fracciones independientemente seleccionadas a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono, alquenilo de 1 a 7 átomos de carbono, alquinilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, halógeno, hidroxi, alcoxilo de 1 a 7 átomos de carbono, feniloxilo, naftiloxilo, fenil- o naftil-alcoxilo de

1 a 7 átomos de carbono, alcanoiloxilo de 1 a 7 átomos de carbono, fenil- o naftil-alcanoiloxilo de 1 a 7 átomos de carbono, amino, mono- o di-(alquilo de 1 a 7 átomos de carbono, fenil, naftil, fenil-alquilo de 1 a 7 átomos de carbono, naftil-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono, y/o fenil- o naftil-alcanoílo de 1 a 7 átomos de carbono)-amino, carboxilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, fenoxi-carbonilo, naftiloxi-carbonilo, fenil-alquiloxilo de 1 a 7 átomos de carbono-carbonilo, naftil-alcoxilo de 1 a 7 átomos de carbono-carbonilo, carbamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, fenil, naftil, fenil-alquilo de 1 a 7 átomos de carbono, y/o naftil-alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, ciano, sulfo, sulfamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, fenil, naftil, fenil-alquilo de 1 a 7 átomos de carbono, y/o naftil-alquilo de 1 a 7 átomos de carbono)-amino-sulfonilo, y nitro, o de preferencia, en donde se mencionan los sustituyentes preferidos, por uno o más de estos sustituyentes mencionados;

R^2 es fenilo, naftilo, o naftil-alquilo de 1 a 7 átomos de carbono, en donde cada fenilo o naftilo mencionados hasta ahora en la definición de R^2 está insustituido o sustituido como justamente se describió para fenilo o naftilo sustituido en la definición de R^1, o es de preferencia cicloalquilo de 3 a 8 átomos de carbono, o es alquilo de 1 a 7 átomos de carbono que está insustituido o sustituido por uno o más, en especial hasta tres, por ejemplo uno o dos sustituyentes independientemente

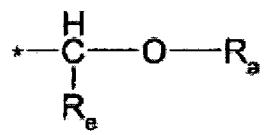
seleccionados a partir del grupo que consiste en alquenilo de 2 a 7 átomos de carbono, alquinilo de 2 a 7 átomos de carbono, halógeno, hidroxi, alcoxilo de 1 a 7 átomos de carbono, halo-alcoxilo de 1 a 7 átomos de carbono, hidroxi-alcoxilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono, fenil- o naftil-oxilo, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono, alcanoiloxilo de 1 a 7 átomos de carbono, (alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, fenilo, y/o fenil-alquilo de 1 a 7 átomos de carbono)-amino-carboniloxilo, benzoil- o naftoil-oxilo, tioalquilo de 1 a 7 átomos de carbono, halo-tioalquilo de 1 a 7 átomos de carbono, tal como trifluoro-tiometilo, hidroxi-tioalquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-tioalquilo de 1 a 7 átomos de carbono, tiofenilo o tionaftilo, fenil- o naftil-tioalquilo de 1 a 7 átomos de carbono, nitro, amino, mono- o di-(alquilo de 1 a 7 átomos de carbono, fenilo, naftilo, fenil-alquilo de 1 a 7 átomos de carbono, naftil-alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, y/o alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono)-amino, alcanoílo de 1 a 7 átomos de carbono-amino, benzoil- o naftoil-amino, fenil- o naftil-alquilo de 1 a 7 átomos de carbono-carbonil-amino, alquilo de 1 a 7 átomos de carbono-sulfonil-amino, fenil- o naftil-sulfonil-amino, en donde el fenilo o naftilo está insustituido o sustituido por una o

más, en especial por una a tres fracciones de alquilo de 1 a 7 átomos de carbono, fenil- o naftil-alquilo de 1 a 7 átomos de carbono-sulfonil-amino, carboxilo, alquilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, fenil- o naftil-oxicarbonilo, fenil- o naftil-alcoxilo de 1 a 7 átomos de carbono-carbonilo, carbamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, N-mono- o N,N-di-(naftil- o fenil-alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, ciano, sulfenilo, sulfonilo, alquilo de 1 a 7 átomos de carbono-sulfinilo, fenil- o naftil-sulfinilo, en donde fenilo o naftilo está insustituido o sustituido por una o más, en especial por una a tres fracciones de alquilo de 1 a 7 átomos de carbono, fenil- o naftil-alquilo de 1 a 7 átomos de carbono-sulfinilo, sulfonilo, alquilo de 1 a 7 átomos de carbono-sulfonilo, fenil- o naftil-sulfonilo, en donde el fenilo o naftilo está insustituido o sustituido por una o más, en especial por una a tres fracciones de alquilo de 1 a 7 átomos de carbono, fenil- o naftil-alquilo de 1 a 7 átomos de carbono-sulfonilo, sulfamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, fenilo, naftilo, fenil-alquilo de 1 a 7 átomos de carbono, o naftil-alquilo de 1 a 7 átomos de carbono)-amino-sulfonilo, N-mono-, N'-mono-, N,N-di-, ó N,N,N'-tri-(alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, fenilo, y/o fenil-alquilo de 1 a 7 átomos de carbono)-amino-carbonil-amino o -amino-carboniloxilo, y N-mono-, N'-mono-, N,N-di-, ó N,N,N'-tri-

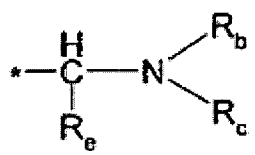
(alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, y/o alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono)-amino-sulfonil-amino; o es cicloalquilo de 3 a 10 átomos de carbono, o ciclo-alquilo de 3 a 10 átomos de carbono-alquilo de 1 a 7 átomos de carbono;

R^3 es una fracción seleccionada a partir del grupo de fracciones de las fórmulas:

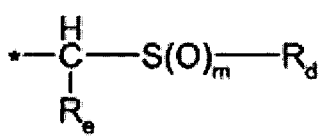
(a)



(b)

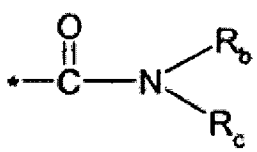


(c)



y

(f)



en donde, en cualquiera de las fracciones de las fórmulas

dadas anteriormente bajo (a), (b), (c), y (f), el asterisco (*) muestra el enlace que enlaza a la fracción R^3 respectiva con el resto de la molécula en la Fórmula I;

R_a es acilo seleccionado a partir de alcanoílo de 1 a 7 átomos de carbono, fenil-alcanoílo de 1 a 7 átomos de carbono insustituido o mono-, di-, o tri-sustituido por (halo-alcoxilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono-alquiloxilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, y/o alquilo de 1 a 7 átomos de carbono), cicloalquilo de 3 a 8 átomos de carbono-carbonilo, o cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono-carbonilo, (tetrahidro-furanil o tetrahidro-piranil)-carbonilo, o (tetrahidrofuranil o tetrahidropiranil)-alquilo de 1 a 7 átomos de carbono-carbonilo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, N-[fenil, o fenil-alquilo de 1 a 7 átomos de carbono]-amino-carbonilo, N-[cicloalquilo de 3 a 8 átomos de carbono o cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono]-amino-carbonilo, alquilo de 1 a 7 átomos de carbono-amino-carbonilo, N-(fenil-alquilo de 1 a 7 átomos de carbono)-(alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, N-(fenil-alquilo de 1 a 7 átomos de carbono)-(cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, N-(alquilo de 1 a 7 átomos de carbono)-(cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, N-(fenil-alquilo de 1 a 7

átomos de carbono)-(cicloalquilo de 3 a 8 átomos de carbono)-amino-carbonilo, N-(heterociclil-alquilo de 1 a 7 átomos de carbono)-(cicloalquilo de 3 a 8 átomos de carbono)-amino-carbonilo, N-(heterociclil)-(ciclo-alquilo de 3 a 8 átomos de carbono)-amino-carbonilo; o es hidrógeno;

R_b es alquilo de 1 a 7 átomos de carbono o fenilo, naftilo, fenil-alquilo de 1 a 7 átomos de carbono, o naftil-alquilo de 1 a 7 átomos de carbono - en cada caso insustituido o sustituido -, en donde, en el caso de una fracción sustituida, los sustituyentes son uno o más, en especial hasta tres sustituyentes independientemente seleccionados a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono, alquenilo de 2 a 7 átomos de carbono, alquinilo de 2 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, tal como trifluoro-metilo, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, amino-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono, hidroxi-alcoxilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono, alcanoiloxilo de 1 a 7 átomos de carbono, amino, mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino, alcanoílo de 1 a 7 átomos de carbono-amino, alquilo de 1 a 7 átomos de carbono-sulfonil-amino, alcoxilo de 1 a 7 átomos de carbono-carbonilo, carboxi-alquilo de 1 a 7 átomos de carbono, halógeno, hidroxi, halo-alcoxilo de 1 a 7 átomos de carbono, halo-tioalquilo de 1 a 7 átomos de carbono, nitro,

carboxilo, alquilo de 1 a 7 átomos de carbono-carbonilo, halo-alquilo de 1 a 7 átomos de carbono-carbonilo, hidroxi-alquilo de 1 a 7 átomos de carbono-carbonilo, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-carbonilo, halo-alcoxilo de 1 a 7 átomos de carbono-carbonilo, carbamoílo, ciano, alquilo de 1 a 7 átomos de carbono-sulfinilo, sulfonilo, alquilo de 1 a 7 átomos de carbono-sulfonilo, halo-alquilo de 1 a 7 átomos de carbono-sulfonilo, hidroxi-alquilo de 1 a 7 átomos de carbono-sulfonilo, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-sulfonilo, sulfamoílo, y N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino-sulfonilo; o es acilo, como justamente se definió bajo R_a, o en particular:

(a) arilo mono- o bi-cíclico-carbonilo insustituido o sustituido, en donde la fracción de arilo se selecciona de preferencia a partir de fenilo, indanilo, indenilo, 1,2,3,4-tetrahidro-naftilo, o naftilo, el cual está insustituido, mono- o di-sustituido por alquilo de 1 a 7 átomos de carbono, -O-alquilo de 1 a 7 átomos de carbono, tal como OMe, halo-alquilo de 1 a 7 átomos de carbono, halógeno, tal como Cl, -O-alquileno de 1 a 7 átomos de carbono-O-alquilo, tal como O-$C_3H_6OCH_3$, hidroxi, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, carboxilo, y ciano, heterociclilo insustituido o sustituido, de preferencia insustituido, o heterociclil-

alquilo de 1 a 4 átomos de carbono insustituido o sustituido, de preferencia insustituido, tal como heterociclilo-CH_2, en donde la fracción de heterociclilo en cada caso es de preferencia heterociclilo monocíclico de 5 ó 6 miembros, que contiene preferiblemente un átomo de N y/u O, tal como tetrahidro-furanilo o tetra-hidro-piranilo, piperidinilo, pirrolidinilo, piperazinilo, o morfolinilo;

(b) heterociclilo mono- o bi-cíclico-carbonilo insustituido o sustituido, en donde la fracción de hetero-ciclilo de preferencia se selecciona a partir de sistemas de anillo de 5 a 11 miembros, los cuales pueden ser saturados, parcialmente saturados, o aromáticos, y tienen de preferencia 1, 2, ó 3 heteroátomos seleccionados a partir de O, N, ó S, incluyendo pirrolidinilo, oxazolilo, pirrolidin-2-onilo, pirrolilo, piperidilo, furanilo, pirimidilo, piridilo, pirazinilo, isoxazolilo, pirrolidin-2-onilo, tetrahidro-furanilo, o tetrahidro-piranilo; indolilo, 2,3-dihidro-benzo-[1,4]-dioxinilo, cromanilo, 2H-cromenilo, 3,4-dihidro-1H-quinolin-2-onilo, benzo-[d]-isoxazolilo, 4,5,6,7-tetrahidro-benzo-[d]-isoxazolilo, 3a,4,5,6, 7,7a-hexahidro-benzo-[d]-isoxazolilo, 1,4,5,6-tetrahidro-ciclo-pentapirazolilo, 3,4-dihidro-2H-benzo-[b]-[1,4]-dioxepinilo, benzofuranilo, 4H-benzo-[1,4]-oxazin-3-onilo, benzo-oxazolilo, benzo-[1,2,5]-oxadiazolilo, bencimidazolilo, ó 3,4-dihidro-2H-benzo-[1,4]-oxazinilo, en donde la fracción de heterociclilo está insustituida o está mono-sustituida con -alquilo de 1 a 7 átomos de carbono, tal como metilo, halógeno, hidroxi, alcanoílo

de 1 a 7 átomos de carbono, fenilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, cicloalquilo de 3 a 8 átomos de carbono insustituido o sustituido, de preferencia insustituido, tal como ciclopropilo, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, carboxilo, y ciano, más preferiblemente fenilo, -alquilo de 1 a 7 átomos de carbono, o cicloalquilo de 3 a 8 átomos de carbono;

(c) cicloalquilo mono- o bi-cíclico-carbonilo insustituido o sustituido, en donde la fracción de cicloalquilo de preferencia se selecciona a partir de cicloalquilo de 3, 4, 5, 6, y 7 átomos de carbono, el cual puede estar insustituido o mono-sustituido por O-alquilo de 1 a 4 átomos de carbono, tal como OMe, halógeno, hidroxi, fenilo insustituido o sustituido, naftilo, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono-amino, carboxilo, y ciano;

(d) alquil-carbonilo insustituido o sustituido, en donde la fracción de alquilo de preferencia se selecciona a partir de alquilo de 1 a 7 átomos de carbono de cadena ramificada o recta, tal como isopropilo, isobutilo, butilo secundario, o butilo terciario, isopentilo, 1-etil-propilo, 2,2-dimetil-propilo, y 1,2-dimetil-propilo,

metilo, etilo, o propilo normal, en donde la fracción de alquilo está insustituida o de preferencia sustituida por O-alquilo de 1 a 4 átomos de carbono, tal como OMe, halógeno, hidroxi, fenil- o naftil-oxilo insustituido o sustituido, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, nitro, amino-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono-amino, tal como -NHCOMe, amino-carbonilo, amino-carbonilo N-mono- o N,N-di-sustituido, tal como CONHMe, carboxilo, alquiloxilo de 1 a 7 átomos de carbono-carbonilo, tal como COOMe, y ciano;

(e) arilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono-carbonilo insustituido o sustituido, tal como aril-CH_2-, aril-CH_2CH_2-, aril-$CH(CH_3)$-, aril-$CH_2CH(CH_3)$-, o aril-$C(CH_3)_2$-, en donde la fracción de alquilo, en particular cuando aril-alquilo es aril-CH_2- o aril-CH_2CH_2-, puede estar mono-sustituida con O-alquilo de 1 a 4 átomos de carbono, tal como OMe, halógeno, hidroxi, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono-amino, tal como -NHCOMe, carboxilo, y ciano, o fenilo insustituido o sustituido, de preferencia insustituido, y en donde la fracción de arilo de preferencia se selecciona a partir de fenilo, indanilo, indenilo, 1,2,3,4-tetra-hidro-naftilo, o naftilo, el cual puede estar insustituido o mono-, di- o tri-sustituido por alquilo de 1 a 7 átomos de carbono, -O-alquilo de 1 a 7 átomos de carbono, tal como OMe, halo-alquilo de 1 a 7 átomos de carbono, tal como CF_3, halógeno, tal como Cl o F, -O-

alquileno de 1 a 7 átomos de carbono-O-alquilo, tal como -O-$C_3H_6OCH_3$, hidroxi, fenilo o naftilo insustituido o sustituido, de preferencia sustituido, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono-amino, tal como -NHCOMe, carboxilo, y ciano;

(f) heterociclilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono-carbonilo insustituido o sustituido, tal como heterociclil-CH_2-, heterociclil-CH_2CH_2-, o heterociclil-$CH_2C(CH_3)_2$-, en donde la fracción de heterociclilo de preferencia se selecciona a partir de sistemas de anillo de 5 a 11 miembros, los cuales pueden ser saturados, parcial-mente saturados, o aromáticos, y tienen de preferencia 1, 2, ó 3 heteroátomos seleccionados a partir de O, N, ó S, en particular pirrolidinilo, oxazolilo, pirimidilo, piridilo, pirazinilo, isoxazolilo, pirrolidin-2-onilo, pirrolilo, piperidilo, furanilo, tetrahidro-furanilo, o tetrahidro-piranilo; 4H-benzo-[1,4]-oxazin-3-onilo, benzo-oxazolilo, indolilo, 2,3-dihidro-benzo-[1,4]-dioxinilo, cromanilo, 2H-cromenilo, 3,4-dihidro-1H-quinolin-2-onilo, benzo[d]isoxazolilo, 4,5,6,7-tetrahidro-benzo[d]isoxazolilo, 3a,4,5,6,7,7a-hexahidro-benzo-[d]-isoxazolilo, 1,4,5,6-tetrahidro-ciclopenta-pirazolilo, 3,4-dihidro-2H-benzo[b][1,4]dioxepinilo, benzofuranilo, benzo-[1,2,5]-oxadiazolilo, bencimidazolilo, ó 3,4-dihidro-2H-benzo-[1,4]-oxazinilo, en donde

la fracción de heterociclilo está insustituida, o está mono-sustituida por -alquilo de 1 a 7 átomos de carbono, tal como metilo, halógeno, hidroxi, alcanoílo de 1 a 7 átomos de carbono, fenilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, cicloalquilo de 3 a 8 átomos de carbono insustituido o sustituido, de preferencia insustituido, tal como ciclopropilo, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, carboxilo, y ciano;

(g) cicloalquilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono-carbonilo insustituido o sustituido, tal como cicloalquil-CH_2-, cicloalquil-CH_2CH_2-, o cicloalquil-$CH_2C(CH_3)_2$-, en donde la fracción de alquilo puede estar mono-sustituida, incluyendo sobre el átomo de carbono en donde se une la fracción de cicloalquilo, con O-alquilo de 1 a 4 átomos de carbono, tal como OMe, halógeno, hidroxi, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, carboxilo, y ciano, y en donde la fracción de cicloalquilo de preferencia se selecciona a partir de cicloalquilo de 3, 5, y 6 átomos de carbono, la cual puede estar insustituida o sustituida por O-alquilo de 1 a 4 átomos de carbono, tal como OMe, halógeno, hidroxi, fenilo insustituido o sustituido, naftilo, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, nitro, amino, amino-alquilo

de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono-amino, tal como -NHCOMe, -NHCOEt, ó $-NHCOCH(CH_3)_2$, carboxilo, y ciano;

(h) alquiloxi-carbonilo insustituido o sustituido, en donde la fracción de alquilo de preferencia se selecciona a partir de alquilo de 1 a 7 átomos de carbono de cadena ramificada o recta, tal como isopropilo, isobutilo, butilo secundario o butilo terciario, isopentilo, 1-etil-propilo, 2,2-dimetil-propilo, y 1,2-dimetil-propilo, metilo, etilo, propilo normal, butilo normal, o pentilo normal, y la cual puede estar insustituida o mono-sustituida por O-alquilo de 1 a 4 átomos de carbono, tal como OMe, halógeno, hidroxi, fenil- o naftil-oxilo insustituido o sustituido, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono-amino, tal como -NHCOMe, amino-carbonilo, amino-carbonilo N-mono- o N,N-di-sustituido, tal como CONHMe, carboxilo, alquiloxilo de 1 a 7 átomos de carbono-carbonilo, tal como COOMe, y ciano;

(i) arilo mono- o bi-cíclico-carbonilo insustituido o sustituido, en donde la fracción de arilo de preferencia se selecciona a partir de fenilo, indanilo, indenilo, 1,2,3,4-tetrahidro-naftilo, o naftilo, la cual puede estar insustituida o mono- o di-sustituida por alquilo de 1 a 7 átomos de carbono, -O-alquilo de 1 a 7 átomos de carbono, tal como OMe, halo-alquilo de 1 a 7 átomos de carbono, halógeno, tal como Cl, -O-alquileno de 1 a 7

átomos de carbono-O-alquilo, tal como O-$C_3H_6OCH_3$, hidroxi, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, carboxilo, y ciano, heterociclilo insustituido o sustituido, de preferencia insustituido, o heterociclil-alquilo de 1 a 4 átomos de carbono insustituido o sustituido, de preferencia insustituido, tal como heterociclil-CH_2, en donde la fracción de heterociclilo en cada caso es de preferencia heterociclilo monocíclico de 5 ó 6 miembros, que preferiblemente contiene un átomo de N y/u O, tal como tetrahidro-furanilo, tetrahidro-piranilo, piperidinilo, pirrolidinilo, pirrolidin-2-onilo, piperazinilo, o morfolinilo;

(j) heterocicliloxilo mono- o bi-cíclico-carbonilo insustituido o sustituido, en donde la fracción de hetero-ciclilo de preferencia se selecciona a partir de sistemas de anillo de 5 a 7 miembros, los cuales pueden ser saturados, parcialmente saturados, o aromáticos, y tienen 1, 2, ó 3 heteroátomos seleccionados a partir de O, N, ó S, en particular pirrolidinilo, oxazolilo, pirrolidin-2-onilo, pirrolilo, piperidilo, furanilo, pirimidilo, piridilo, pirazinilo, isoxazolilo, pirrolidin-2-onilo, tetrahidro-furanilo, o tetrahidro-piranilo; de una manera más preferible tetra-hidro-furanilo o tetrahidro-piranilo, en donde la fracción de heterociclilo está insustituida o mono-sustituida por -alquilo de 1 a 7 átomos de carbono, tal como metilo, halógeno, hidroxi, alcanoílo

de 1 a 7 átomos de carbono, fenilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, cicloalquilo de 3 a 8 átomos de carbono insustituido o sustituido, de preferencia insustituido, tal como ciclopropilo, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, carboxilo, y ciano;

(k) cicloalquilo mono- o bi-cíclico-oxicarbonilo insustituido o sustituido, en donde la fracción de cicloalquilo de preferencia se selecciona a partir de cicloalquilo de 3, 4, 5, 6, y 7 átomos de carbono, la cual puede estar sustituida o insustituida por O-alquilo de 1 a 4 átomos de carbono, tal como OMe, halógeno, hidroxi, fenilo insustituido o sustituido, naftilo, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono-amino, carboxilo, y ciano;

(l) arilo mono- o bi-cíclico-alquiloxilo de 1 a 7 átomos de carbono-carbonilo insustituido o sustituido, tal como aril-CH_2-, aril-CH_2CH_2-, aril-$CH(CH_3)$-, aril-$CH_2CH(CH_3)$- o aril-$CH(CH_2CH_3)$-, en donde la fracción de arilo se selecciona de preferencia a partir de fenilo, indanilo, indenilo, 1,2,3,4-tetrahidro-naftilo, o naftilo, la cual puede estar insustituida o mono-sustituida por alquilo de 1 a

7 átomos de carbono, -O-alquilo de 1 a 7 átomos de carbono, tal como OMe, halo-alquilo de 1 a 7 átomos de carbono, tal como CF_3, halógeno, tal como Cl ó F, -O-alquileno de 1 a 7 átomos de carbono-O-alquilo, tal como $O\text{-}C_3H_6OCH_3$, hidroxi, fenilo o naftilo insustituido o sustituido, de preferencia sustituido, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono-amino, tal como -NHCOMe, carboxilo, y ciano;

(m) heterociclilo mono- o bi-cíclico-alquiloxilo de 1 a 7 átomos de carbono-carbonilo insustituido o sustituido, tal como heterociclil-CH_2-, heterociclil-CH_2CH_2-, o hetero-ciclil-$CH_2CH(CH_3)$-, en donde la fracción de cicloalquilo de preferencia se selecciona a partir de sistemas de anillo de 5 a 7 miembros, los cuales pueden ser saturados, parcialmente saturados, o aromáticos, y tienen 1, 2, ó 3 heteroátomos seleccionados a partir de O, N, ó S, tales como pirrolidinilo, oxazolilo, pirimidilo, piridilo, pirazinilo, isoxazolilo, pirrolidin-2-onilo, pirrolilo, piperidilo, furanilo, 1,3-dioxano, tetrahidro-furanilo, o tetrahidro-piranilo; en donde la fracción de heterociclilo puede estar insustituida o sustituida por -alquilo de 1 a 7 átomos de carbono, tal como metilo, halógeno, hidroxi, alcanoílo de 1 a 7 átomos de carbono, tal como COMe, fenilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido,

fenil- o naftil-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, cicloalquilo de 3 a 8 átomos de carbono insustituido o sustituido, de preferencia insustituido, tal como ciclopropilo, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, carboxilo, y ciano;

(n) cicloalquilo mono- o bi-cíclico-oxicarbonilo de 1 a 7 átomos de carbono insustituido o sustituido, tal como cicloalquil-CH_2-, cicloalquil-CH_2CH_2-, o cicloalquil-$CH_2CH(CH_3)$-, más preferiblemente cicloalquil-CH_2-, en donde la fracción de cicloalquilo de preferencia se selecciona a partir de cicloalquilo de 3 y 5 átomos de carbono, y puede estar insustituida o sustituida por O-alquilo de 1 a 4 átomos de carbono, tal como OMe, halógeno, hidroxi, fenilo insustituido o sustituido, naftilo, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono-amino, tal como -NHCOMe, -NHCOEt, ó $-NHCOCH(CH_3)_2$, carboxilo, y ciano;

(o) N-mono- o N,N-di-(arilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido

o sustituido, y/o alquilo insustituido o sustituido)-amino-carbonilo, en donde:

- la fracción de alquilo del alquil-amino-carbonilo insustituido o sustituido es de preferencia alquilo de 1 a 7 átomos de carbono de cadena ramificada o recta, tal como isopropilo, isobutilo, butilo secundario o butilo terciario, isopentilo, 1-etil-propilo, 2,2-dimetil-propilo, y 1,2-dimetil-propilo, metilo, etilo, propilo normal, butilo normal, o pentilo normal, la cual está insustituida o sustituida por O-alquilo de 1 a 4 átomos de carbono, tal como OMe, halógeno, hidroxi, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono-amino, tal como -NHCOMe, amino-carbonilo, amino-carbonilo N-mono- o N,N-di-sustituido, tal como CONHMe, carboxilo, alquiloxilo de 1 a 7 átomos de carbono-carbonilo, tal como COOMe, y ciano;

- la fracción de arilo del aril-amino-carbonilo insustituido o sustituido es de preferencia fenilo, indanilo, indenilo, 1,2,3,4-tetrahidro-naftilo, o naftilo, la cual está insustituida o mono-sustituida por alquilo de 1 a 7 átomos de carbono, -O-alquilo de 1 a 7 átomos de carbono, tal como OMe, halo-alquilo de 1 a 7 átomos de carbono, tal como Cl, -O-alquileno de 1 a 7 átomos de carbono-O-alquilo, tal como O-$C_3H_6OCH_3$, hidroxi, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o

naftil-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, carboxilo, y ciano;

- la fracción de ciclo-alquilo del cicloalquil-amino-carbonilo insustituido o sustituido es de preferencia ciclo-alquilo de 3 a 6 átomos de carbono, la cual puede estar insustituida o sustituida por O-alquilo de 1 a 4 átomos de carbono, tal como OMe, halógeno, hidroxi, fenilo insustituido o sustituido, naftilo, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono-amino, carboxilo, y ciano;

- la fracción de aril-alquilo del aril-alquil-amino-carbonilo insustituido o sustituido es de preferencia aril-CH_2-, aril-CH_2CH_2-, o aril-$CH(CH_2CH_3)$-, en donde la fracción de alquilo, en particular cuando el aril-alquilo es aril-CH_2-, puede estar mono-sustituida por O-alquilo de 1 a 4 átomos de carbono, tal como OMe, halógeno, hidroxi, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono-amino, tal como -NHCOMe, carboxilo, y ciano, o fenilo insustituido o sustituido, de preferencia insustituido, y en donde la fracción de arilo es de preferencia fenilo, indanilo, indenilo, 1,2,3,4-tetrahidro-naftilo, o naftilo, la cual está insustituida, mono-, di-, o tri-sustituida por alquilo de 1 a 7 átomos de carbono, -O-alquilo de 1 a 7 átomos de carbono, tal

como OMe, halo-alquilo de 1 a 7 átomos de carbono, tal como CF_3, halógeno, tal como Cl ó F, -O-alquileno de 1 a 7 átomos de carbono-O-alquilo, tal como $O\text{-}C_3H_6OCH_3$, hidroxi, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono-amino, tal como -NHCOMe, carboxilo, y ciano;

- la fracción de heterociclil-alquilo del heterociclil-alquil-amino-carbonilo insustituido o sustituido es de preferencia heterociclil-CH_2- o heterociclil-CH_2CH_2-, en donde la fracción de heterociclilo se selecciona de preferencia a partir de sistemas de anillo de 5 a 7 miembros, los cuales pueden ser anillos aromáticos o saturados, y tienen 1, 2, ó 3 heteroátomos seleccionados a partir de O, N, ó S, tales como pirrolidinilo, oxazolilo, pirimidilo, piridilo, pirazinilo, isoxazolilo, pirrolidin-2-onilo, pirrolilo, piperidilo, furanilo, 1,3-dioxano, tetrahidro-furanilo, o tetrahidro-piranilo; que pueden estar insustituidos o mono-sustituidos por -alquilo de 1 a 7 átomos de carbono, tal como metilo, halógeno, hidroxi, alcanoílo de 1 a 7 átomos de carbono, tal como COMe, fenilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, cicloalquilo de 3 a 8 átomos de carbono insustituido o sustituido, de preferencia insustituido, tal como ciclopropilo, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, carboxilo, y ciano;

- la fracción de ciclo-alquil-alquilo del cicloalquil-alquil-

amino-carbonilo insustituido o sustituido es de preferencia cicloalquil-CH_2-, en donde la fracción de cicloalquilo se selecciona de preferencia a partir de cicloalquilo de 6 átomos de carbono, la cual puede estar insustituida o mono-sustituida por O-alquilo de 1 a 4 átomos de carbono, tal como OMe, halógeno, hidroxi, fenilo insustituido o sustituido, naftilo, fenil- o naftil-oxilo insustituido o sustituido, de preferencia insustituido, fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono insustituido o sustituido, de preferencia insustituido, nitro, amino, amino-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono-amino, tal como -NHCOMe, -NHCOEt, ó -$NHCOCH(CH_3)_2$, carboxilo, y ciano;

cuando R_b es acilo, R_c es como se define en la presente, de preferencia R_c es hidroxi-alquilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, o de preferencia hidrógeno, ciclo-alquilo de 3 a 8 átomos de carbono insustituido o sustituido, o alquilo de 1 a 7 átomos de carbono insustituido o sustituido, más preferiblemente ciclopropilo o metilo. En particular, cuando R_b es acilo como se define en (h) a (n), R_c es de preferencia hidrógeno, cicloalquilo de 3 a 8 átomos de carbono insustituido o sustituido, o cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, o alquilo de 1 a 7 átomos de carbono insustituido o sustituido, más preferiblemente ciclopropilo o metilo; en particular,

cuando R_b es acilo como se define en (o), R_c es de preferencia cicloalquilo de 3 a 8 átomos de carbono insustituido o sustituido, más preferible-mente ciclopropilo;

o R_b se selecciona a partir de (fenil- o fenil-alquilo de 1 a 7 átomos de carbono)-sulfonilo insustituido o mono-, di-, o tri-sustituido por (halógeno y/o alquilo de 1 a 7 átomos de carbono), alquilo de 1 a 7 átomos de carbono-sulfonilo;

R_c es hidroxi-alquilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, o de preferencia hidrógeno, cicloalquilo de 3 a 8 átomos de carbono insustituido o sustituido, o alquilo de 1 a 7 átomos de carbono insustituido o sustituido;

R_d es fenil- o naftil-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, en donde, en el caso de una fracción sustituida, los sustituyentes son uno o más, en especial hasta tres sustituyentes independientemente seleccionados a partir de aquéllos mencionados para fenil- o naftil-alquilo de 1 a 7 átomos de carbono insustituido o sustituido bajo R_b, o es $-N(R_b)(R_c)$;

R_e es alquilo de 1 a 7 átomos de carbono, o de preferencia hidrógeno; y

m es 2;

cada uno de R^4 y R^5 se selecciona, independiente-mente uno del otro, a partir de alquilo de 1 a 7 átomos de carbono, hidroxi, alquiloxilo de 1 a 7 átomos de carbono, y de preferencia

hidrógeno;

y T es carbonilo, o de preferencia metileno;

o una sal del mismo.

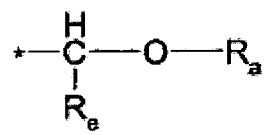
12. Un compuesto de la Fórmula I de acuerdo con la reivindicación 5, en donde:

R^1 es fenil-, indolil-, quinolil- ó 2,3-dihidro-benzo-[1,4]-dioxinil-alcanoílo de 1 a 7 átomos de carbono (de preferencia -carbonilo o -acetilo), en donde el fenilo, indolilo, quinolilo, ó 2,3-dihidro-benzo-[1,4]-dioxinilo está sustituido por halógeno, alquiloxilo de 1 a 7 átomos de carbono-alquiloxilo de 1 a 7 átomos de carbono, alquileno de 1 a 7 átomos de carbono-O-alquilo de 1 a 7 átomos de carbono, o alquiloxilo de 1 a 7 átomos de carbono-alquiloxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, y además puede estar sustituido por una o más fracciones de alquilo de 1 a 7 átomos de carbono (en especial, metilo), y/o alquiloxilo de 1 a 7 átomos de carbono;

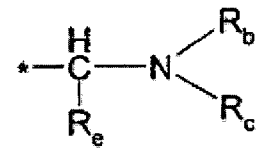
R^2 es cicloalquilo de 3 a 8 átomos de carbono, o de preferencia alquilo de 1 a 7 átomos de carbono;

R^3 es una fracción seleccionada a partir del grupo de facciones de las fórmulas:

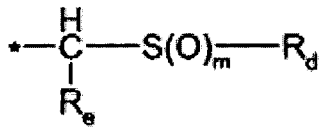
(a)



(b)

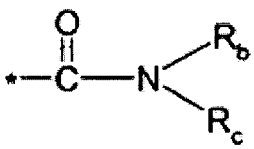


(c)



y

(f)



en donde, en cualquiera de las fracciones de las fórmulas dadas anteriormente bajo (a), (b), (c), y (f), el asterisco (*) muestra el enlace que enlaza a la fracción R^3 respectiva con el resto de la molécula en la Fórmula I,

en donde:

R_a es hidrógeno, o N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, fenilo o naftilo (insustituido o sustituido por halógeno), fenil-alquilo de 1 a 7 átomos de carbono, naftil-alquilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono, heterociclil-alquilo de 1 a 7 átomos de carbono, (heterociclil y/o cicloalquilo de 3 a 8 átomos de carbono)-amino-carbonilo;

cada uno de R_b y R_c, independientemente uno del otro, se selecciona a partir de hidrógeno, alquilo de 1 a 7 átomos de

carbono, cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono, arilo insustituido o sustituido tal como fenilo, naftilo, naftil-alquilo de 1 a 7 átomos de carbono, o acilo, tal como cicloalquilo de 3 a 8 átomos de carbono-carbonilo, cicloalquilo de 3 a 8 átomos de carbono-alquilo de 1 a 7 átomos de carbono-carbonilo, fenil- o naftil-alcanoílo de 1 a 7 átomos de carbono insustituido o mono-, di-, o tri-sustituido por (halógeno, alcoxilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono-alquiloxilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, y/o alquilo de 1 a 7 átomos de carbono), (tetrahidrofuranil o tetrahidro-piranil)-carbonilo, o (tetrahidrofuranil o tetrahidropiranil)-alquilo de 1 a 7 átomos de carbono-carbonilo, alquilo de 1 a 7 átomos de carbono-sulfonilo, o (fenil- o naftil)-alquilo de 1 a 7 átomos de carbono-sulfonilo (insustituido o sustituido por [alquilo de 1 a 7 átomos de carbono, halo-alquilo inferior, halógeno, alquiloxilo de 1 a 7 átomos de carbono, ciano, alcanoílo de 1 a 7 átomos de carbono, y/o alquilo de 1 a 7 átomos de carbono-sulfonilo]),

en particular, acilo se selecciona a partir de:

(a) arilo mono- o bi-cíclico-carbonilo insustituido o sustituido, en donde la fracción de arilo se selecciona de preferencia a partir de fenilo, indanilo, ó 1,2,3,4-tetrahidro-naftilo, el cual está insustituido, mono- o di-sustituido por heterociclilo mono- o di- sustituido, heterociclilo-CH_2, -O-alquilo de 1 a 7

átomos de carbono, -O-alquileno de 1 a 7 átomos de carbono-O-alquilo, y/o halógeno, en donde la fracción de heterociclilo en cada caso es de preferencia heterociclilo monocíclico de 5 ó 6 miembros, que contiene preferiblemente un átomo de N y/u O, tal como tetrahidro-furanilo o tetra-hidro-piranilo, piperidinilo, pirrolidinilo, piperazinilo, o morfolinilo;

(b) heterociclilo mono- o bi-cíclico-carbonilo insustituido o sustituido, en donde la fracción de hetero-ciclilo de preferencia se selecciona a partir de sistemas de anillo de 5 a 11 miembros, los cuales pueden ser saturados, parcialmente saturados, o aromáticos, y tienen de preferencia 1 ó 2 heteroátomos seleccionados a partir de O y/o N, incluyendo pirazinilo, isoxazolilo, pirrolidin-2-onilo, tetrahidro-furanilo, tetrahidro-piranilo; indolilo, 2,3-dihidro-benzo-[1,4]-dioxinilo, cromanilo, 2H-cromenilo, 3,4-dihidro-1H-quinolin-2-onilo, benzo-[d]-isoxazolilo, 4,5,6,7-tetrahidro-benzo-[d]-isoxazolilo, 3a,4,5,6,7,7a-hexahidro-benzo-[d]-isoxazolilo, 1,4,5,6-tetrahidro-ciclo-pentapirazolilo, 3,4-dihidro-2H-benzo-[b]-[1,4]-dioxepinilo, en donde la fracción de heterociclilo está insustituida o está mono-sustituida con fenilo, alquilo de 1 a 7 átomos de carbono, o cicloalquilo de 3 a 8 átomos de carbono insustituido;

(c) cicloalquilo mono- o bi-cíclico-carbonilo insustituido o sustituido, en donde la fracción de cicloalquilo de preferencia se selecciona a partir de cicloalquilo de 3, 4, 5, 6, y 7 átomos de carbono, el cual puede estar insustituido o mono-sustituido por O-

alquilo de 1 a 4 átomos de carbono, o hidroxi;

(d) alquil-carbonilo insustituido o sustituido, en donde la fracción de alquilo de preferencia se selecciona a partir de alquilo de 1 a 7 átomos de carbono de cadena ramificada o recta, tal como isobutilo, isopentilo, y 2,2-dimetil-propilo, metilo, etilo, o propilo normal, en donde la fracción de alquilo está mono-sustituida por O-alquilo de 1 a 7 átomos de carbono, hidroxi, alcanoílo de 1 a 7 átomos de carbono-amino, feniloxilo insustituido o di-sustituido, amino-carbonilo, amino-carbonilo N-mono- o N,N-di-sustituido, y alquiloxilo de 1 a 7 átomos de carbono-carbonilo;

(e) arilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono-carbonilo insustituido o sustituido, tal como aril-CH_2-, aril-CH_2CH_2-, aril-$CH(CH_3)$-, aril-$CH_2CH(CH_3)$-, o aril-$C(CH_3)_2$-, en donde la fracción de alquilo, en particular cuando aril-alquilo es aril-CH_2- o aril-CH_2CH_2-, puede estar mono-sustituida con fenilo, alcanoílo de 1 a 7 átomos de carbono-amino, -O-alquilo de 1 a 4 átomos de carbono, o hidroxi, y en donde la fracción de arilo de preferencia se selecciona a partir de fenilo o naftilo, la cual puede estar insustituida o sustituida por -O-alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono-amino, fenilo sustituido, alcanoílo de 1 a 7 átomos de carbono-amino, y/o halógeno;

(f) heterociclilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono-carbonilo insustituido o sustituido, tal como heterociclil-CH_2-, heterociclil-CH_2CH_2-, o heterociclil-$CH_2C(CH_3)_2$-,

en donde la fracción de heterociclilo de preferencia se selecciona a partir de sistemas de anillo de 5 a 11 miembros, los cuales pueden ser saturados, parcial-mente saturados, o aromáticos, y tienen de preferencia 1 ó 2 heteroátomos seleccionados a partir de O y/o N, en particular pirrolidinilo, pirrolidin-2-onilo, pirrolilo, piperidilo, furanilo, tetrahidro-furanilo, o tetrahidro-piranilo; 4H-benzo-[1,4]-oxazin-3-onilo o benzo-oxazolilo, en donde la fracción de heterociclilo está insustituida, o está mono-sustituida por fenilo insustituido, alquilo de 1 a 7 átomos de carbono, o alcanoílo de 1 a 7 átomos de carbono;

(g) cicloalquilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono-carbonilo insustituido o sustituido, tal como cicloalquil-CH_2-, en donde la fracción de alquilo puede estar mono-sustituida, incluyendo sobre el átomo de carbono en donde se une la fracción de cicloalquilo, con -alquilo de 1 a 4 átomos de carbono o hidroxi, y en donde la fracción de cicloalquilo de preferencia se selecciona a partir de cicloalquilo de 3, 5, y 6 átomos de carbono, la cual puede estar insustituida o sustituida por amino, O-alquilo de 1 a 4 átomos de carbono, o hidroxi;

(h) alquiloxi-carbonilo insustituido o sustituido, en donde la fracción de alquilo de preferencia se selecciona a partir de alquilo de 1 a 7 átomos de carbono de cadena ramificada o recta, tal como isobutilo, isopentilo, y 2,2-dimetil-propilo, metilo o etilo, y la cual puede estar mono-sustituida por O-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono-amino, y amino-

carbonilo N-mono- o N,N-di-sustituido;

(i) arilo mono- o bi-cíclico-carbonilo insustituido o sustituido, en donde la fracción de arilo de preferencia se selecciona a partir de fenilo o naftilo, la cual puede estar insustituida o mono-sustituida por heterociclilo u -O-alquilo de 1 a 7 átomos de carbono, en donde la fracción de heterociclilo es heterociclilo monocíclico de 5 ó 6 miembros, que contiene un átomo de N y/u O, tal como tetrahidro-furanilo, tetrahidro-piranilo, piperidinilo, pirrolidinilo, pirrolidin-2-onilo, piperazinilo, o morfolinilo;

(j) heterocicliloxilo mono- o bi-cíclico-carbonilo insustituido o sustituido, en donde la fracción de hetero-ciclilo de preferencia se selecciona a partir de sistemas de anillo de 5 a 7 miembros, los cuales pueden ser saturados, parcialmente saturados, o aromáticos, y tienen 1 ó 2 heteroátomos seleccionados a partir de O y/o N, en particular tetrahidro-furanilo, o tetrahidro-piranilo; de una manera más preferible tetra-hidro-furanilo o tetrahidro-piranilo, en donde la fracción de heterociclilo está insustituida;

(k) cicloalquilo mono- o bi-cíclico-oxicarbonilo insustituido o sustituido, en donde la fracción de cicloalquilo de preferencia se selecciona a partir de cicloalquilo de 6 átomos de carbono, la cual está insustituida;

(l) arilo mono- o bi-cíclico-alquiloxilo de 1 a 7 átomos de carbono-carbonilo insustituido o sustituido, tal como aril-CH_2-, aril-

CH_2CH_2-, aril-$CH(CH_3)$-, aril-$CH_2CH(CH_3)$- o aril-$CH(CH_2CH_3)$-, en donde la fracción de arilo se selecciona de preferencia a partir de fenilo, la cual está insustituida;

(m) heterociclilo mono- o bi-cíclico-alquiloxilo de 1 a 7 átomos de carbono-carbonilo insustituido o sustituido, tal como heterociclil-CH_2-, heterociclil-CH_2CH_2-, o hetero-ciclil-$CH_2CH(CH_3)$-, en donde la fracción de cicloalquilo de preferencia se selecciona a partir de sistemas de anillo de 5 a 7 miembros, los cuales pueden ser saturados, parcialmente saturados, o aromáticos, y tienen 1 ó 2 heteroátomos seleccionados a partir de O y/o N, tales como piridilo, piperidilo, isoxazolilo, tetrahidro-furanilo, tetrahidro-piranilo, o 1,3-dioxano, la cual está insustituida o está mono-sustituida por -alquilo de 1 a 7 átomos de carbono o alcanoílo de 1 a 7 átomos de carbono;

(n) cicloalquilo mono- o bi-cíclico-oxicarbonilo de 1 a 7 átomos de carbono insustituido o sustituido, tal como cicloalquil-CH_2-, en donde la fracción de cicloalquilo de preferencia se selecciona a partir de cicloalquilo de 3 y 5 átomos de carbono, y puede estar insustituida o sustituida por alcanoílo de 1 a 7 átomos de carbono-amino;

(o) N-mono- o N,N-di-(arilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, cicloalquilo

mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, y/o alquilo insustituido o sustituido)-amino-carbonilo, en donde:

- la fracción de alquilo del alquil-amino-carbonilo insustituido o sustituido es de preferencia alquilo de 1 a 7 átomos de carbono de cadena ramificada o recta, tal como isopropilo, isobutilo, metilo, o etilo, la cual está insustituida;

- la fracción de arilo del aril-amino-carbonilo insustituido o sustituido es de preferencia fenilo o naftilo, la cual está insustituida;

- la fracción de ciclo-alquilo del cicloalquil-amino-carbonilo insustituido o sustituido es de preferencia ciclo-alquilo de 3 a 6 átomos de carbono, la cual está insustituida;

- la fracción de aril-alquilo del aril-alquil-amino-carbonilo insustituido o sustituido es de preferencia aril-CH_2-, aril-CH_2CH_2-, o aril-$CH(CH_2CH_3)$-, en donde la fracción de alquilo, en particular cuando el aril-alquilo es aril-CH_2-, puede estar mono-sustituida por fenilo insustituido, y en donde la fracción de arilo es de preferencia fenilo, la cual está insustituida;

- la fracción de heterociclil-alquilo del heterociclil-alquil-amino-carbonilo insustituido o sustituido es de preferencia heterociclil-CH_2-, en donde la fracción de heterociclilo se selecciona de preferencia a partir de sistemas de anillo de 5 a 7 miembros, los cuales pueden ser anillos aromáticos o saturados, y tienen 1 ó 2 heteroátomos seleccionados a partir de O y/o N, tales

como furanilo o tetrahidro-piranilo; la cual está insustituida;

- la fracción de ciclo-alquil-alquilo del cicloalquil-alquil-amino-carbonilo insustituido o sustituido es de preferencia cicloalquil-CH_2-, en donde la fracción de cicloalquilo se selecciona de preferencia a partir de cicloalquilo de 6 átomos de carbono, la cual está insustituida;

con la condición de que si R_c es hidrógeno, alquilo de 1 a 7 átomos de carbono, fenilo, naftilo, o naftil-alquilo de 1 a 7 átomos de carbono, entonces R_b también puede ser fenil-alquilo de 1 a 7 átomos de carbono;

R_d es (fenil- o naftil)-alquilo de 1 a 7 átomos de carbono insustituido o sustituido por [alquilo de 1 a 7 átomos de carbono, fenilo, halo-alquilo inferior, halógeno, oxo-alquilo de 1 a 7 átomos de carbono, alquiloxilo de 1 a 7 átomos de carbono, fenil-alcoxilo de 1 a 7 átomos de carbono, halo-alquiloxilo de 1 a 7 átomos de carbono, fenoxilo, alcanoílo de 1 a 7 átomos de carbono-amino, ciano, alcanoílo de 1 a 7 átomos de carbono, y/o alquilo de 1 a 7 átomos de carbono-sulfonilo];

R_e es hidrógeno; y

m es 2;

cada uno de R^4 y R^5 es hidrógeno; y

T es carbonilo, o de preferencia metileno;

o una sal del mismo.

13. Un compuesto de la Fórmula I de acuerdo con la reivindicación 5, seleccionado a partir del grupo de compuestos:

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N-((3S*,4S*)-4-{[(3-acetil-amino-3-metil-butiril)-ciclopropil-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S*,4S*)-4-({ciclopropil-[2-(2-oxo-pirrolidin-1-il)-acetil]-amino}-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S*,4S*)-4-({[2-(1-acetil-amino-ciclopentil)-acetil]-ciclopropil-amino}-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S*,4S*)-4-{[ciclopropil-(3,3-dimetil-butiril)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S*,4S*)-4-({[2-(1-acetil-amino-ciclohexil)-acetil]-ciclopropil-amino}-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S*,4S*)-4-{[ciclopropil-(3-metil-3-pirrol-1-il-butiril)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S*,4S*)-4-({ciclopropil-[2-(3-oxo-3,4-dihidro-2H-benzo-[1,4]-oxazin-6-il)-acetil]-amino}-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S*,4S*)-4-({ciclopropil-[2-(1-isobutiril-amino-ciclopentil)-acetil]-amino}-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S*,4S*)-4-{[ciclopropil-(4-metil-pentanoil)-amino]-

metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S*,4S*)-4-({ciclopropil-[2-(2-metil-benzo-oxazol-5-il)-acetil]-amino}-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S*,4S*)-4-{[(3-ciclohexil-propionil)-ciclopropil-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[ciclopropil-(3-ciclopropil-propionil)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[(3-ciclopentil-propionil)-ciclopropil-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[ciclopropil-(3,3-difenil-propionil)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-[(3S,4S)-4-({ciclopropil-[2-(2,6-dimetil-fenoxi)-acetil]-amino}-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[ciclopropil-((S)-3-fenil-butiril)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-[(3S,4S)-4-({[2-(1-acetil-piperidin-4-il)-acetil]-ciclopropil-amino}-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-

propoxi)-benzamida,

N-((3S,4S)-4-{[((S)-3-acetil-amino-3-fenil-propionil)-ciclopropil-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[((R)-3-acetil-amino-3-fenil-propionil)-ciclopropil-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[ciclopropil-((R)-3-hidroxi-3-fenil-propionil)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[ciclopropil-((S)-3-hidroxi-3-fenil-propionil)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[ciclopropil-(3-furan-2-il-propionil)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[ciclopropil-(2-furan-2-il-acetil)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[ciclopropil-((S)-2-metoxi-2-ciclohexil-acetil)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[ciclopropil-((S)-2-hidroxi-4-metil-pentanoil)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-{(3S*,4S*)-4-[(ciclohexan-carbonil-ciclopropil-amino)-metil]-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

ciclopropil-[(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido cicloheptan-carboxílico,

N-((3S,4S)-4-{[(2-ciclopentil-acetil)-ciclopropil-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S*,4S*)-4-{[(2-ciclohexil-acetil)-ciclopropil-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-{(3S*,4S*)-4-[(benzoil-ciclopropil-amino)-metil]-pirrolidin-3-ilmetil}-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-[(3S*,4S*)-4-({ciclopropil-[2-(4-fluoro-fenil)-acetil]-amino}-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-[(3S,4S)-4-({[2-(4-cloro-fenil)-acetil]-ciclopropil-amino}-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-[(3S*,4S*)-4-({[2-cloro-fenil)-acetil]-ciclopropil-amino}-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-[(3S*,4S*)-4-({ciclopropil-[2-(2-metoxi-fenil)-acetil]-amino}-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-

propoxi)-benzamida,

N-[(3S*,4S*)-4-({ciclopropil-[2-(3,5-difluoro-fenil)-acetil]-amino}-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-[(3S*,4S*)-4-({ciclopropil-[2-(2,3,5-trifluoro-fenil)-acetil]-amino}-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-[(3S*,4S*)-4-({ciclopropil-[2-(3-trifluoro-metil-fenil)-acetil]-amino}-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-[(3S*,4S*)-4-({[2-(3,5-bis-trifluoro-metil-fenil)-acetil]-ciclopropil-amino}-metil)-pirrolidin-3-ilmetil]-N-iso-propil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S*,4S*)-4-{[ciclopropil-(3-pirrolidin-1-il-benzoil)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-[(3S*,4S*)-4-({ciclopropil-[2-(3'-fluoro-bifenil-3-il)-acetil]-amino}-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S*,4S*)-4-{[ciclopropil-(3-cloro-6-metoxi-1-il-benzoil)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S*,4S*)-4-{[ciclopropil-(4-morfolin-4-ilmetil-benzoil)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

ciclopropil-[(3S*,4S*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido 1H-indol-2-carboxílico,

ciclopropil-[(3S*,4S*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido 1H-indol-3-carboxílico,

ciclopropil-[(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido 2,3-dihidro-benzo[1,4]-dioxin-6-carboxílico,

N-((3S*,4S*)-4-{[ciclopropil-(2-naftalen-2-il-acetil)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[ciclopropil-(2-fenoxi-acetil)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S*,4S*)-4-{[ciclopropil-((S)-2-fenil-propionil)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S*,4S*)-4-{[ciclopropil-((R)-2-fenil-propionil)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[ciclopropil-((S)-2-hidroxi-2-fenil-acetil)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[ciclopropil-((R)-2-hidroxi-2-fenil-acetil)-

amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[ciclopropil-((R)-2-metoxi-2-fenil-acetil)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[ciclopropil-((S)-2-metoxi-2-fenil-acetil)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

ciclopropil-[(3S*,4S*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido tetrahidro-furan-3-carboxílico,

ciclopropil-[(3S*,4S*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido tetrahidro-furan-2-carboxílico,

ciclopropil-[(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido (S)-tetrahidro-piran-3-carboxílico,

ciclopropil-[(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido (R)-tetrahidro-piran-3-carboxílico,

ciclopropil-[(3S*,4S*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido tetrahidro-piran-4-carboxílico,

N-((3S,4S)-4-{[ciclopropil-(4-hidroxi-ciclohexan-carbonil)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-

propoxi)-benzamida,

N-((3S,4S)-4-{[ciclopropil-(cis-4-metoxi-ciclohexan-carbonil)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[ciclopropil-(trans-4-metoxi-ciclohexan-carbonil)-amino]-metil}-pirrolidin-3-ilmetil)-N-iso-propil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[ciclopropil-((S)-2-tetrahidro-furan-2-il-acetil)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[ciclopropil-((R)-2-tetrahidro-furan-2-il-acetil)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[ciclopropil-((S)-2-tetrahidro-piran-2-il-acetil)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[ciclopropil-((R)-2-tetrahidro-piran-2-il-acetil)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

ciclopropil-[(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido (R)-1,2,3,4-tetrahidro-naftalen-2-carboxílico,

ciclopropil-[(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido (S)-1,2,3,4-tetrahidro-naftalen-2-carboxílico,

N-((3S*,4S*)-4-{[ciclopropil-(2-tetrahidro-piran-4-il-acetil)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

ciclopropil-[(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido croman-2-carboxílico,

ciclopropil-[(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido 2H-cromen-3-carboxílico,

ciclopropil-[(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido (R)-2,3-dihidro-benzo-[1,4]-dioxin-2-carboxílico,

ciclopropil-[(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido (S)-2,3-dihidro-benzo-[1,4]-dioxin-2-carboxílico,

ciclopropil-[(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido 2-oxo-1,2,3,4-tetrahidro-quinolin-4-carboxílico,

ciclopropil-[(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido 4,5,6,7-tetrahidro-benzo-[d]-isoxazol-3-carboxílico,

ciclopropil-[(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido 3a,4,5,6,7,7a-hexahidro-benzo[d]-isoxazol-3-carboxílico,

N-((3S,4S)-4-{[(2-benzo[d]-isoxazol-3-il-acetil)-ciclopropil-

amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

ciclopropil-[(3S*,4S*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido 1,4,5,6-tetrahidro-ciclopenta-pirazol-3-carboxílico,

ciclopropil-[(3S*,4S*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido isoxazol-3-carboxílico,

ciclopropil-[(3S*,4S*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido 5-metil-isoxazol-3-carboxílico,

ciclopropil-[(3S*,4S*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido 5-ciclopropil-isoxazol-3-carboxílico,

ciclopropil-[(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido 5-fenil-isoxazol-3-carboxílico,

ciclopropil-[(3S*,4S*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido 5-metil-pirazin-2-carboxílico,

ciclopropil-[(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido indan-2-carboxílico,

ciclopropil-[(3S*,4S*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido

5-oxo-1-fenil-pirrolidin-3-carboxílico,

N-ciclopropil-[(3S*,4S*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-succinamida,

N-ciclopropil-[(3S*,4S*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-N'-metil-succinamida,

metil-éster del ácido N-ciclopropil-[(3S*,4S*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-succinámico,

N-((3S,4S)-4-{[ciclopropil-(2-piperidin-4-il-acetil)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-[(3S,4S)-4-({[2-(4-amino-ciclohexil)-acetil]-ciclo-propil-amino}-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-[(3S,4S)-4-({[2-(4-amino-ciclohexil)-acetil]-ciclo-propil-amino}-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[ciclopropil-(2-metil-2-fenil-propionil)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[((S)-2-hidroxi-2-fenil-acetil)-metil-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[((S)-2-metoxi-2-fenil-acetil)-metil-amino]-

metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[((S)-2-hidroxi-4-metil-pentanoil)-metil-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[((S)-2-metoxi-2-ciclohexil-acetil)-metil-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[((S)-2-hidroxi-3-metil-butiril)-metil-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[((S)-2-hidroxi-3-metil-butiril)-metil-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[((S)-2-hidroxi-3-fenil-propionil)-metil-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[((S)-2-ciclohexil-2-hidroxi-acetil)-metil-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[((S)-3-hidroxi-3-fenil-propionil)-metil-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[((R)-3-hidroxi-3-fenil-propionil)-metil-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-

propoxi)-benzamida,

N-((3S,4S)-4-{[(2-furan-2-il-acetil)-metil-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[((S)-2-metoxi-3-metil-butiril)-metil-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[((S)-2-metoxi-4-metil-pentanoil)-metil-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-{(3S*,4S*)-4-[(benzoil-metil-amino)-metil]-pirrolidin-3-ilmetil}-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[(2-ciclohexil-acetil)-metil-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-isopropil-4-metoxi-N-[(3S*,4S*)-4-({[2-(3-metoxi-fenil)-acetil]-metil-amino}-metil)-pirrolidin-3-ilmetil]-3-(3-metoxi-propoxi)-benzamida,

[(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-metil-amida del ácido indan-2-carboxílico,

[(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-metil-amida del ácido (R)-1,2,3,4-tetrahidro-naftalen-2-carboxílico,

[(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-

benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-metil-amida del ácido (S)-1,2,3,4-tetrahidro-naftalen-2-carboxílico,

[(3S*,4S*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-metil-amida del ácido tetrahidro-piran-4-carboxílico,

N-[(3S,4S)-4-({[2-(1-hidroxi-ciclohexil)-acetil]-metil-amino}-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-isopropil-4-metoxi-N-[(3S,4S)-4-({[2-(4-metoxi-ciclohexil)-acetil]-metil-amino}-metil)-pirrolidin-3-ilmetil]-3-(3-metoxi-propoxi)-benzamida,

N-isopropil-4-metoxi-N-[(3S,4S)-4-({[2-(4-metoxi-ciclohexil)-acetil]-metil-amino}-metil)-pirrolidin-3-ilmetil]-3-(3-metoxi-propoxi)-benzamida,

[(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-metil-amida del ácido 3,4-dihidro-2H-benzo[b][1,4]dioxepin-2-carboxílico,

N-isopropil-4-metoxi-N-((3S,4S)-4-{[(cis-4-metoxi-ciclohexan-carbonil)-metil-amino]-metil}-pirrolidin-3-ilmetil)-3-(3-metoxi-propoxi)-benzamida,

N-isopropil-4-metoxi-N-((3S,4S)-4-{[(trans-4-metoxi-ciclohexan-carbonil)-metil-amino]-metil}-pirrolidin-3-ilmetil)-3-(3-metoxi-propoxi)-benzamida,

N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-N-[(3S,4S)-4-(fenil-acetil-amino-metil)-pirrolidin-3-ilmetil]-benzamida,

[(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido indan-2-carboxílico,

N-{(3S,4S)-4-[((S)-2-ciclohexil-2-metoxi-acetil-amino)-metil]-pirrolidin-3-ilmetil}-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-isopropil-4-metoxi-N-[(3S,4S)-4-[((R)-2-metoxi-2-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-3-(3-metoxi-propoxi)-benzamida,

N-isopropil-4-metoxi-N-{(3S,4S)-4-[((S)-2-metoxi-2-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-3-(3-metoxi-propoxi)-benzamida,

N-{(3S,4S)-4-[((R)-2-ciclohexil-2-metoxi-acetil-amino)-metil]-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-{(3S,4S)-4-[(etil-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[etil-(2-tetrahidro-piran-4-il-acetil)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-{(3S*,4S*)-4-[(ciclobutil-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S*,4S*)-4-{[ciclobutil-(2-tetrahidro-piran-4-il-acetil)-amino]-metil-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-

propoxi)-benzamida,

N-isopropil-N-{(3S*,4S*)-4-[(isopropil-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-isopropil-N-((3S*,4S*)-4-{[isopropil-(2-tetrahidro-piran-4-il-acetil)-amino]-metil}-pirrolidin-3-ilmetil}-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-{(3S*,4S*)-4-[(ciclopropan-carbonil-isobutil-amino)-metil]-pirrolidin-3-ilmetil}-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-{(3S*,4S*)-4-[(ciclobutan-carbonil-isobutil-amino)-metil]-pirrolidin-3-ilmetil}-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S*,4S*)-4-{[isobutil-(2-tetrahidro-piran-4-il-acetil)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-{(3S*,4S*)-4-[(isobutil-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-{(3S*,4S*)-4-[(ciclopropil-metil-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-((3S*,4S*)-4-{[ciclopropil-metil-(2-tetrahidro-piran-4-il-acetil)-amino]-metil}-pirrolidin-3-ilmetil)-N-iso-propil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

isopropil-{(3S,4S)-4-[(metil-fenil-acetil-amino)-metil]-

pirrolidin-3-ilmetil}-amida del ácido 1-(3-metoxi-propil)-3-metil-1H-indol-6-carboxílico,

((3S,4S)-4-{[(2-ciclohexil-acetil)-metil-amino]-metil}-pirrolidin-3-ilmetil)-isopropil-amida del ácido 1-(3-metoxi-propil)-3-metil-1H-indol-6-carboxílico,

N-{(3S,4S)-4-[(ciclopropil-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-4-etil-N-isopropil-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[(2-ciclohexil-acetil)-metil-amino]-metil}-pirrolidin-3-ilmetil)-4-etil-N-isopropil-3-(3-metoxi-propoxi)-benzamida,

4-etil-N-isopropil-3-(3-metoxi-propoxi)-N-((3S,4S)-4-{[metil-(2-tetrahidro-piran-4-il-acetil)-amino]-metil}-pirrolidin-3-ilmetil)-benzamida,

[(3S,4S)-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-3-ilmetil]-metil-amida del ácido tetrahidropiran-4-carboxílico,

N-((3S,4S)-4-{[ciclopropil-(2-tetrahidro-piran-4-il-acetil)-amino]-metil}-pirrolidin-3-ilmetil)-4-etil-N-isopropil-3-(3-metoxi-propoxi)-benzamida,

ciclopropil-[(3S,4S)-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido tetrahidro-piran-4-carboxílico,

N-((3S,4S)-4-{[(3-acetil-amino-3-metil-butiril)-ciclopropil-amino]-metil}-pirrolidin-3-ilmetil)-4-etil-N-iso-propil-3-(3-metoxi-

propoxi)-benzamida,

4-etil-N-((3S,4S)-4-{[((S)-2-hidroxi-2-fenil-acetil)-metil-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-3-(3-metoxi-propoxi)-benzamida,

N-[(3S,4S)-4-({[2-(1-acetil-piperidin-4-il)-acetil]-ciclopropil-amino}-metil)-pirrolidin-3-ilmetil]-4-etil-N-iso-propil-3-(3-metoxi-propoxi)-benzamida,

N-[(3S,4S)-4-({[2-(1-acetil-piperidin-4-il)-acetil]-metil-amino}-metil)-pirrolidin-3-ilmetil]-4-etil-N-isopropil-3-(3-metoxi-propoxi)-benzamida,

4-etil-N-((3S,4S)-4-{[((S)-2-hidroxi-4-metil-pentanoil)-metil-amino]-metil}-pirrolidin-3-ilmetil)-N-iso-propil-3-(3-metoxi-propoxi)-benzamida,

4-etil-N-((3S,4S)-4-{[((S)-2-hidroxi-3-metil-butiril)-metil-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-3-(3-metoxi-propoxi)-benzamida,

[(3S,4S)-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido indan-2-carboxílico,

4-etil-N-isopropil-3-(3-metoxi-propoxi)-N-{(3S,4S)-4-[(2-metil-2-fenil-propionil-amino)-metil]-pirrolidin-3-ilmetil}-benzamida,

4-etil-N-isopropil-N-{(3S,4S)-4-[((R)-2-metoxi-2-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-3-(3-metoxi-propoxi)-benzamida,

4-etil-N-[(3S,4S)-4-({[2-(1-hidroxi-ciclohexil)-acetil]-metil-amino}-metil)-pirrolidin-3-ilmetil]-N-isopropil-3-(3-metoxi-propoxi)-

benzamida,

N-{(3S,4S)-4-({[2-(4-amino-ciclohexil)-acetil]-metil-amino}-metil)-pirrolidin-3-ilmetil]-4-etil-N-isopropil-3-(3-metoxi-propoxi)-benzamida,

N-[(3S,4S)-4-({[2-(4-amino-ciclohexil)-acetil]-metil-amino}-metil)-pirrolidin-3-ilmetil]-4-etil-N-isopropil-3-(3-metoxi-propoxi)-benzamida,

[(3S,4S)-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-3-ilmetil]-metil-amida del ácido 5-metil-pirazin-2-carboxílico,

[(3S,4S)-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-3-ilmetil]-metil-amida del ácido (S)-2,3-dihidro-benzo[1,4]dioxin-2-carboxílico,

[(3S,4S)-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-3-ilmetil]-metil-amida del ácido (R)-2-oxo-1,2,3,4-tetrahidro-quinolin-4-carboxílico,

[(3S,4S)-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-3-ilmetil]-metil-amida del ácido (S)-2-oxo-1,2,3,4-tetrahidro-quinolin-4-carboxílico,

N-ciclopropil-N-[(3S,4S)-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-3-ilmetil]-N'-metil-succinamida,

ciclopropil-[(3S,4S)-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido 5-metil-pirazin-2-carboxílico,

ciclopropil-[(3S,4S)-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido isoxazol-3-carboxílico,

N-[(3S,4S)-4-({[2-(4-amino-ciclohexil)-acetil]-ciclo-propil-amino}-metil)-pirrolidin-3-ilmetil]-4-etil-N-isopropil-3-(3-metoxi-propoxi)-benzamida,

N-[(3S,4S)-4-({[2-(4-amino-ciclohexil)-acetil]-ciclo-propil-amino}-metil)-pirrolidin-3-ilmetil]-4-etil-N-isopropil-3-(3-metoxi-propoxi)-benzamida,

ciclopropil-[(3S,4S)-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido (R)-tetrahidro-furan-3-carboxílico,

ciclopropil-[(3S,4S)-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido (S)-tetrahidro-furan-3-carboxílico,

ciclopropil-[(3S,4S)-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido (R)-tetrahidro-piran-3-carboxílico,

ciclopropil-[(3S,4S)-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido (S)-tetrahidro-piran-3-carboxílico,

N-((3S,4S)-4-{[ciclopropil-(cis-4-hidroxi-ciclohexan-carbonil)-amino]-metil}-pirrolidin-3-ilmetil)-4-etil-N-isopropil-3-(3-metoxi-propoxi)-benzamida,

N-((3S,4S)-4-{[ciclopropil-(trans-4-hidroxi-ciclo-hexan-

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carbonil)-amino]-metil}-pirrolidin-3-ilmetil)-4-etil-N-isopropil-3-(3-metoxi-propoxi)-benzamida,

[(3S,4S)-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-3-ilmetil]-metil-amida del ácido (S)-tetrahidro-piran-3-carboxílico,

[(3S,4S)-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-3-ilmetil]-metil-amida del ácido (R)-tetrahidro-piran-3-carboxílico,

N-isopropil-3-(3-metoxi-propoxi)-4-metil-N-{(3S,4S)-4-[(metil-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-benzamida,

[(3S,4S)-4-({isopropil-[3-(3-metoxi-propoxi)-4-metil-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-metil-amida del ácido tetrahidro-piran-4-carboxílico,

N-isopropil-3-(3-metoxi-propoxi)-4-metil-N-((3S,4S)-4-{[metil-(2-tetrahidro-piran-4-il-acetil)-amino]-metil}-pirrolidin-3-ilmetil)-benzamida,

N-((3S,4S)-4-{[ciclopropil-((S)-2-metoxi-2-fenil-acetil)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-3-(3-metoxi-propoxi)-4-metil-benzamida,

ciclopropil-[(3S,4S)-4-({isopropil-[3-(3-metoxi-propoxi)-4-metil-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido (S)-2,3-dihidro-benzo[1,4]dioxin-2-carboxílico,

N-((3S,4S)-4-{[((S)-2-metoxi-2-fenil-acetil)-metil-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-3-(3-metoxi-propoxi)-4-metil-benzamida,

[(3S,4S)-4-({isopropil-[3-(3-metoxi-propoxi)-4-metil-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-metil-amida del ácido (S)-2,3-dihidro-benzo[1,4]dioxin-2-carboxílico,

N-((3S,4S)-4-{[(3-acetil-amino-3-metil-butiril)-ciclo-propil-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-3-(3-metoxi-propoxi)-4-metil-benzamida,

N-((3S,4S)-4-{[((S)-2-hidroxi-2-fenil-acetil)-metil-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-3-(3-metoxi-propoxi)-4-metil-benzamida,

ciclopropil-[(3S,4S)-4-({isopropil-[3-(3-metoxi-propoxi)-4-metil-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido tetrahidro-piran-4-carboxílico,

N-isopropil-3-(3-metoxi-propoxi)-4-metil-N-[(3S,4S)-4-({metil-[2-(3-oxo-3,4-dihidro-2H-benzo[1,4]oxazin-6-il)-acetil]-amino}-metil)-pirrolidin-3-ilmetil]-benzamida,

N-[(3S,4S)-4-({ciclopropil-[2-(3-oxo-3,4-dihidro-2H-benzo[1,4]oxazin-6-il)-acetil]-amino}-metil)-pirrolidin-3-il-metil]-N-isopropil-3-(3-metoxi-propoxi)-4-metil-benzamida,

N-((3S,4S)-4-{[ciclopropil-(2-tetrahidro-piran-4-il-acetil)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-3-(3-metoxi-propoxi)-4-metil-benzamida,

N-((3S,4S)-4-{[((S)-2-ciclohexil-2-metoxi-acetil)-ciclopropil-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-3-(3-metoxi-propoxi)-4-metil-benzamida,

N-((3S,4S)-4-{[((S)-2-ciclohexil-2-metoxi-acetil)-metil-

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amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-3-(3-metoxi-propoxi)-4-metil-benzamida,

N-((3S,4S)-4-{[((S)-2-hidroxi-3-metil-butiril)-metil-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-3-(3-metoxi-propoxi)-4-metil-benzamida,

N-[(3S,4S)-4-({[2-(1-acetil-piperidin-4-il)-acetil]-ciclopropil-amino}-metil)-pirrolidin-3-ilmetil]-N-isopropil-3-(3-metoxi-propoxi)-4-metil-benzamida,

N-((3S,4S)-4-{[((S)-2-hidroxi-4-metil-pentanoil)-metil-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-3-(3-metoxi-propoxi)-4-metil-benzamida,

N-((3S,4S)-4-{[(cis-4-hidroxi-ciclohexan-carbonil)-metil-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-3-(3-metoxi-propoxi)-4-metil-benzamida,

N-((3S,4S)-4-{[((R)-3-hidroxi-3-fenil-propionil)-metil-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-3-(3-metoxi-propoxi)-4-metil-benzamida,

N-((3S,4S)-4-{[((S)-3-hidroxi-3-fenil-propionil)-metil-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-3-(3-metoxi-propoxi)-4-metil-benzamida,

N-[(3S,4S)-4-({[2-(1-acetil-piperidin-4-il)-acetil]-metil-amino}-metil)-pirrolidin-3-ilmetil]-N-isopropil-3-(3-metoxi-propoxi)-4-metil-benzamida,

N-((3S,4S)-4-{[ciclopropil-(cis-4-hidroxi-ciclohexan-carbonil)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-3-(3-metoxi-

propoxi)-4-metil-benzamida,

N-((3S,4S)-4-{[((S)-2-hidroxi-3-fenil-propionil)-metil-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-3-(3-metoxi-propoxi)-4-metil-benzamida,

N-((3S,4S)-4-{[2-furan-2-il-acetil)-metil-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-3-(3-metoxi-propoxi)-4-metil-benzamida,

N-((3S,4S)-4-{[ciclopropil-((S)-2-hidroxi-4-metil-pentanoil)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-3-(3-metoxi-propoxi)-4-metil-benzamida,

[(3S,4S)-4-({isopropil-[3-(3-metoxi-propoxi)-4-metil-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido indan-2-carboxílico,

N-isopropil-3-(3-metoxi-propoxi)-4-metil-N-{[3S,4S)-4-[(2-metil-2-fenil-propionil-amino)-metil]-pirrolidin-3-ilmetil}-benzamida,

N-isopropil-3-(3-metoxi-propoxi)-4-metil-N-{(3S,4S)-4-[(2-tetrahidro-piran-4-il-acetil-amino)-metil]-pirrolidin-3-ilmetil}-benzamida,

[(3S,4S)-4-({isopropil-[3-(3-metoxi-propoxi)-4-metil-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido (S)-2,3-dihidro-benzo[1,4]dioxin-2-carboxílico,

N-isopropil-3-(3-metoxi-propoxi)-4-metil-N-((3S,4S)-4-{[metil-((R)-2-tetrahidro-piran-2-il-acetil)-amino]-metil}-pirrolidin-3-ilmetil)-benzamida,

N-isopropil-3-(3-metoxi-propoxi)-4-metil-N-((3S,4S)-4-

{[metil-((S)-2-tetrahidro-piran-2-il-acetil)-amino]-metil}-pirrolidin-3-ilmetil)-benzamida,

N-((3S,4S)-4-{[ciclopropil-((R)-2-tetrahidro-furan-2-il-acetil)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-3-(3-metoxi-propoxi)-4-metil-benzamida,

N-((3S,4S)-4-{[ciclopropil-((S)-2-tetrahidro-furan-2-il-acetil)-amino]-metil}-pirrolidin-3-ilmetil)-N-isopropil-3-(3-metoxi-propoxi)-4-metil-benzamida,

N-isopropil-N-((3S,4S)-4-{[(cis-4-metoxi-ciclohexan-carbonil)-metil-amino]-metil}-pirrolidin-3-ilmetil)-3-(3-metoxi-propoxi)-4-metil-benzamida,

N-isopropil-N-((3S,4S)-4-{[(trans-4-metoxi-ciclo-hexan-carbonil)-metil-amino]-metil}-pirrolidin-3-ilmetil)-3-(3-metoxi-propoxi)-4-metil-benzamida,

N-isopropil-N-((3S,4S)-4-{[(cis-4-metoxi-ciclohexan-carbonil)-amino]-metil}-pirrolidin-3-ilmetil)-3-(3-metoxi-propoxi)-4-metil-benzamida,

N-isopropil-N-((3S,4S)-4-{[(trans-4-metoxi-ciclo-hexan-carbonil)-amino]-metil}-pirrolidin-3-ilmetil)-3-(3-metoxi-propoxi)-4-metil-benzamida,

isopropil-{(3S,4S)-4-[(metil-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-amida del ácido 1-(3-metoxi-propil)-1H-indol-6-carboxílico,

N-ciclopropil-N-{(3S,4S)-4-[(ciclopropil-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-4-metoxi-3-(3-metoxi-propoxi)-

benzamida,

bencil-éster del ácido ciclopropil-[(3S,4S)-4-({ciclo-propil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil}-carbámico,

isobutil-éster del ácido ciclopropil-[(3S,4S)-4-({ciclopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

tetrahidro-piran-4-il-éster del ácido ciclopropil-[(3S,4S)-4-({ciclopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

bencil-éster del ácido ciclopropil-[(3S*,4S*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

bencil-éster del ácido ciclopropil-[(3S,4S)-4-({iso-propil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

isobutil-éster del ácido ciclopropil-[(3S*,4S*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

piridin-4-ilmetil-éster del ácido ciclopropil-[(3S*,4S*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

1-metil-piperidin-4-ilmetil-éster del ácido ciclo-propil-[(3S*,4S*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

2-metoxi-etil-éster del ácido ciclopropil-[(3S*,4S*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

tetrahidro-piran-4-ilmetil-éster del ácido ciclo-propil-[(3S*,4S*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

2,2-dimetil-propil-éster del ácido ciclopropil-[(3S*,4S*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

1-metil-ciclopropil-metil-éster del ácido ciclopropil-[(3S*,4S*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

2-acetil-amino-2-metil-propil-éster del ácido ciclo-propil-[(3S*,4S*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

fenil-éster del ácido ciclopropil-[(3S*,4S*)-4-({iso-propil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

2-metil-2-metil-carbamoil-propil-éster del ácido ciclopropil-[(3S*,4S*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

1-acetil-amino-ciclopentil-metil-éster del ácido ciclopropil-[(3S*,4S*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

1-acetil-piperidin-4-ilmetil-éster del ácido ciclo-propil-

[(3S*,4S*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

5-metil-isoxazol-3-ilmetil-éster el ácido ciclopropil-[(3S*,4S*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

naftalen-1-il-éster del ácido ciclopropil-[(3S*,4S*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

ciclopropil-metil-éster del ácido ciclopropil-[(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

isobutil-éster del ácido ciclopropil-[(3S,4S)-4-({iso-propil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

4-metoxi-fenil-éster del ácido ciclopropil-[(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

ciclohexil-éster del ácido ciclopropil-[(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

naftalen-2-il-éster del ácido ciclopropil-[(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

tetrahidro-piran-4-il-éster del ácido ciclopropil-[(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-

pirrolidin-3-ilmetil]-carbámico,

5-metil-[1,3]-dioxan-5-ilmetil-éster del ácido ciclo-propil-[(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

3-(2-oxo-pirrolidin-1-il)-fenil-éster del ácido ciclo-propil-[(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

3-morfolin-4-ilfenil-éster del ácido ciclopropil-[(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

(R)-1-(tetrahidro-furan-2-il)-metil-éster del ácido ciclopropil-[(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

(R)-1-fenil-propil-éster del ácido ciclopropil-[(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

(R)-1-fenil-etil-éster del ácido ciclopropil-[(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

fenil-éster del ácido ciclopropil-[(3S,4S)-4-({iso-propil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

2-metoxi-fenil-éster del ácido ciclopropil-[(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

3-metoxi-3-metil-butil-éster del ácido ciclopropil-[(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

(R)-(tetrahidro-furan-3-il)-éster del ácido ciclo-propil-[(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

(S)-(tetrahidro-furan-3-il)-éster del ácido ciclo-propil-[(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

3-metoxi-3-metil-butil-éster del ácido [(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-metil-carbámico,

tetrahidro-piran-4-il-éster del ácido [(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-metil-carbámico,

tetrahidro-piran-4-il-éster del ácido ciclopropil-[(3S,4S)-4-({isopropil-[3-(3-metoxi-propoxi)-4-metil-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

(S)-tetrahidro-furan-3-il)-éster el ácido ciclopropil-[(3S,4S)-4-({isopropil-[3-(3-metoxi-propoxi)-4-metil-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

tetrahidro-piran-4-il-éster del ácido [(3S,4S)-4-({isopropil-[3-(3-metoxi-propoxi)-4-metil-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-metil-carbámico,

(S)-tetrahidro-furan-3-il)-éster del ácido [(3S,4S)-4-

({isopropil-[3-(3-metoxi-propoxi)-4-metil-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-metil-carbámico,

3-metoxi-3-metil-butil-éster del ácido [(3S,4S)-4-({isopropil-[3-(3-metoxi-propoxi)-4-metil-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-metil-carbámico,

3-metoxi-3-metil-butil-éster del ácido ciclopropil-[(3S,4S)-4-({isopropil-[3-(3-metoxi-propoxi)-4-metil-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

4-metoxi-fenil-éster del ácido [(3S,4S)-4-({iso-propil-[3-(3-metoxi-propoxi)-4-metil-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-metil-carbámico,

(R)-1-(tetrahidro-furan-2-il)-metil-éster del ácido [(3S,4S)-4-({isopropil-[3-(3-metoxi-propoxi)-4-metil-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-metil-carbámico,

4-metoxi-fenil-éster del ácido ciclopropil-[(3S,4S)-4-({isopropil-[3-(3-metoxi-propoxi)-4-metil-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

(R)-1-(tetrahidro-furan-2-il)-metil-éster del ácido ciclopropil-[(3S,4S)-4-({isopropil-[3-(3-metoxi-propoxi)-4-metil-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

5-metil-[1,3]-dioxan-5-ilmetil-éster del ácido [(3S,4S)-4-({isopropil-[3-(3-metoxi-propoxi)-4-metil-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-metil-carbámico,

5-metil-isoxazol-3-ilmetil-éster del ácido ciclo-propil-[(3S,4S)-4-({isopropil-[3-(3-metoxi-propoxi)-4-metil-benzoil]-

amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

5-metil-isoxazol-3-ilmetil-éster del ácido [(3S,4S)-4-({isopropil-[3-(3-metoxi-propoxi)-4-metil-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-metil-carbámico,

bencil-éster del ácido ciclopropil-[(3S,4S)-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

tetrahidro-piran-4-il-éster del ácido ciclopropil-[(3S,4S)-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

4-metoxi-fenil-éster del ácido ciclopropil-[(3S,4S)-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

tetrahidro-piran-4-il-éster del ácido [(3S,4S)-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-3-ilmetil]-metil-carbámico,

(R)-1-(tetrahidro-furan-2-il)-metil-éster del ácido [(3S,4S)-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-3-ilmetil]-metil-carbámico,

(S)-(tetrahidro-furan-3-il)-éster del ácido [(3S,4S)-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-3-ilmetil]-metil-carbámico,

5-metil-[1,3]dioxan-5-ilmetil-éster del ácido [(3S,4S)-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-3-ilmetil]-metil-carbámico,

3-metoxi-3-metil-butil-éster del ácido [(3S,4S)-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-3-ilmetil]-metil-carbámico,

bencil-éster del ácido ciclopropil-[(3S,4S)-4-({isopropil-[1-(3-metoxi-propil)-3-metil-1H-indol-6-carbonil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

isobutil-éster del ácido ciclopropil-[(3S,4S)-4-({isopropil-[1-(3-metoxi-propil)-3-metil-1H-indol-6-carbonil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

tetrahidro-piran-4-il-éster del ácido ciclopropil-[(3S,4S)-4-({isopropil-[1-(3-metoxi-propil)-3-metil-1H-indol-6-carbonil]-amino}-metil)-pirrolidin-3-ilmetil]-carbámico,

(3S*,4S*)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil-éster del ácido bencil-metil-carbámico,

(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil-éster del ácido di-isobutil-carbámico,

(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil-éster del ácido bencil-ciclopropil-carbámico,

(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil-éster del ácido isobutil-metil-carbámico,

(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-

benzoil]-amino}-metil)-pirrolidin-3-ilmetil-éster del ácido ciclopropil-(tetrahidro-piran-4-ilmetil)-carbámico,

(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil-éster del ácido ciclopropil-(tetrahidro-piran-4-il)-carbámico,

(3S,4S)-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-3-ilmetil-éster del ácido ciclohexil-metil-metil-carbámico,

(3S,4S)-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-3-ilmetil-éster del ácido bencil-ciclopropil-carbámico,

(3S,4S)-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-3-ilmetil-éster del ácido ciclopropil-(tetrahidro-piran-4-ilmetil)-carbámico,

(3S,4S)-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-3-ilmetil-éster del ácido ciclopropil-(tetrahidro-piran-3-ilmetil)-carbámico,

(3S,4S)-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-3-ilmetil-éster del ácido ciclopropil-(tetrahidro-piran-4-il)-carbámico,

(3S,4S)-4-({[4-etil-3-(3-metoxi-propoxi)-benzoil]-isopropil-amino}-metil)-pirrolidin-3-ilmetil-éster del ácido ciclopropil-(tetrahidro-piran-2-ilmetil)-carbámico,

(3S,4S)-4-({isopropil-[1-(3-metoxi-propil)-3-metil-1H-indol-6-carbonil]-amino}-metil)-pirrolidin-3-ilmetil-éster del ácido

ciclopropil-(tetrahidro-piran-4-il)-carbámico,

(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil-éster del ácido ((R)-1-fenil-propil)-carbámico,

N-[(3S*,4S*)-4-(1-ciclopropil-3-furan-2-ilmetil-ureido-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-[(3S,4S)-4-(1-ciclopropil-3-furan-2-ilmetil-ureido-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-[(3S*,4S*)-4-(3-(4-metoxi-bencil-1-ciclopropil-ureido-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-[(3S*,4S*)-4-(3-(4-cloro-bencil-1-ciclopropil-ureido-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-[(3S*,4S*)-4-(3-(4-fluoro-bencil-1-ciclopropil-ureido-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-[(3S*,4S*)-4-(3-ciclohexil-metil-1-ciclopropil-ureido-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-[(3S*,4S*)-4-[1-ciclopropil-3-(tetrahidro-piran-4-ilmetil)-ureido-metil]-pirrolidin-3-ilmetil}-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-[(3S*,4S*)-4-(1-ciclopropil-3-fenetil-ureido-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-[(3S*,4S*)-4-(1-ciclopropil-3,3-difenil-ureido-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-[(3S*,4S*)-4-(1-ciclopropil-3,3-di-isopropil-ureido-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-[(3S*,4S*)-4-(3-bencil-1-ciclopropil-3-metil-ureido-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-[(3S*,4S*)-4-(3-bencil-1-ciclopropil-3-etil-ureido-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-[(3S,4S)-4-(3-bencil-1-ciclopropil-3-etil-ureido-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-[(3S*,4S*)-4-(3-bencil-1,3-diciclopropil-ureido-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-[(3S*,4S*)-4-(1-ciclopropil-3-fenil-ureido-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-[(3S*,4S*)-4-(3-benz-hidril-1-ciclopropil-ureido-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-

benzamida,

N-[(3S,4S)-4-(3-bencil-1-ciclopropil-ureido-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-[(3S*,4S*)-4-(1,3-diciclopropil-3-fenil-ureido-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-[(3S*,4S*)-4-(3-ciclohexil-1-ciclopropil-ureido-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-[3S*,4S*)-4-(1-ciclopropil-3-naftalen-1-il-ureido-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-[(3S,4S)-4-(1-ciclopropil-3-naftalen-2-il-ureido-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-{3S,4S)-4-[1-ciclopropil-3-((R)-1-fenil-propil)-ureido-metil]-pirrolidin-3-ilmetil}-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-[(3S,4S)-4-(1-ciclopropil-3-isobutil-3-metil-ureido-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

N-{3S,4S)-4-[1-ciclopropil-3-((S)-1-fenil-propil)-ureido-metil]-pirrolidin-3-ilmetil}-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

ciclopropil-[(3S,4S)-4-({isopropil-[4-metoxi-3-(3-metoxi-

propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-amida del ácido (R)-3-fenil-pirrolidin-1-carboxílico,

4-etil-3-(3-hidroxi-propoxi)-N-isopropil-N-{(3S,4S)-4-[(metil-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-benzamida,

N-{(3S,4S)-4-[(ciclopropil-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-3-(3-hidroxi-propoxi)-N-isopropil-4-metoxi-benzamida,

N-{(3S*,4S*)-4-[(ciclopropil-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-N-isopropil-4-metoxi-3-(4-metoxi-butil)-benzamida,

N-{(3S*,4S*)-4-[(ciclopropil-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-4-difluoro-metil-N-isopropil-3-(3-metoxi-propoxi)-benzamida,

{(3S*,4S*)-4-[(ciclopropil-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-isopropil-amida del ácido 8-(3-metoxi-propoxi)-2,3-dihidro-benzo-[1,4]-dioxin-6-carboxílico,

N-{(3S*,4S*)-4-[(ciclopropil-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-N-isopropil-4-metoxi-5-(3-metoxi-propoxi)-2-metil-benzamida,

2-cloro-N-{(3S*,5S*)-4-[(ciclopropil-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-N-isopropil-4-metoxi-5-(3-metoxi-propoxi)-benzamida,

3-cloro-N-{(3S*,4S*)-4-[(ciclopropil-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-N-isopropil-5-(3-metoxi-propoxi)-benzamida,

4-cloro-N-{(3S*,4S*)-4-[(ciclopropil-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-N-isopropil-3-(3-metoxi-propoxi)-benzamida,

4-terbutil-N-isopropil-3-(3-metoxi-propoxi)-N-{(3S,4S)-4-[(metil-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-benzamida,

N-isopropil-4-metoxi-3-(2-metoxi-etoxi-metil)-N-{(3S,4S)-4-[(metil-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-benzamida,

N-isopropil-3-(2-metoxi-etoxi-metil)-N-{(3S,4S)-4-[(metil-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-4-tri-fluoro-metoxi-benzamida,

N-isopropil-4-metoxi-N-{(3S,4S)-4-[(metil-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-3-(3,3,3-trifluoro-propoxi)-benzamida,

N-isopropil-4-metoxi-N-{(3S,4S)-4-[(metil-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-3-(4,4,4-trifluoro-butoxi)-benzamida,

N-{(3S,4S)-4-[(ciclopropil-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-N-isopropil-4-metoxi-3-(3-trifluoro-metoxi-propoxi)-benzamida,

N-{(3S,4S)-4-[(ciclopropil-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-4-etil-N-isopropil-3-(3-trifluoro-metoxi-propoxi)-benzamida,

N-isopropil-4-metoxi-3-(5-metil-isoxazol-3-il-metoxi)-N-{(3S,4S)-4-[(metil-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-benzamida,

N-{(3S,4S)-4-[(ciclopropil-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-N-isopropil-3-(2-metoxi-etoxi-metil)-4-trifluoro-metoxi-benzamida,

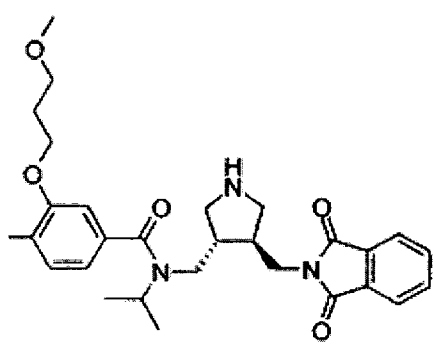
3-(2-etoxi-etoxi)-N-isopropil-4-metoxi-N-{(3S,4S)-4-[(metil-fenil-acetil-amino)-metil]-pirrolidin-3-ilmetil}-benzamida,

N-[(3S*,4S*)-4-({ciclopropil-[2-(4-metoxi-fenil)-acetil]-amino}-metil)-pirrolidin-3-ilmetil]-N-isopropil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

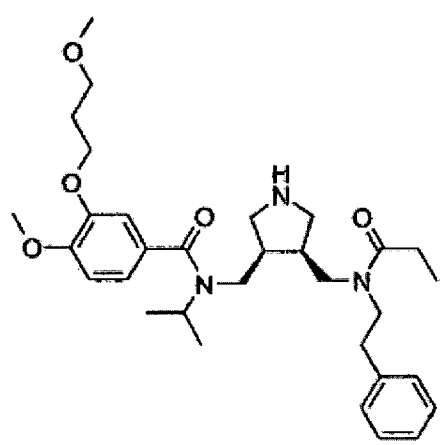
N-[(3S*,4S*)-4-({ciclopropil-[4-metoxi-3-(3-metoxi-propoxi)-benzoil]-amino}-metil)-pirrolidin-3-ilmetil]-N-iso-propil-4-metoxi-3-(3-metoxi-propoxi)-benzamida,

o una sal farmacéuticamente aceptable de los mismos.

14. Un compuesto de la Fórmula:



ó



15. Un compuesto de la Fórmula I, o una sal farmacéuticamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 5 a 7 u 11 a 14, para utilizarse en el diagnóstico o en el tratamiento terapéutico de un animal de

sangre caliente.

16. Un compuesto de la Fórmula I, o una sal farmacéuticamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 5 a 7 u 11 a 14, para utilizarse de acuerdo con la reivindicación 15, en el tratamiento de una enfermedad que dependa de la actividad de la renina, en especial hipertensión.

17. El uso de un compuesto de la Fórmula I, o una sal farmacéuticamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 5 a 7 u 11 a 14, para la fabricación de una composición farmacéutica para el tratamiento de una enfermedad que dependa de la actividad de la renina, en especial hipertensión.

18. El uso de un compuesto de la Fórmula I, o una sal farmacéuticamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 5 a 7 u 11 a 14, para el tratamiento de una enfermedad que dependa de la actividad de la renina, en especial hipertensión.

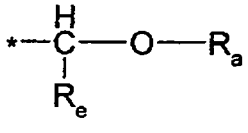
19. Una formulación farmacéutica, la cual comprende un compuesto de la Fórmula I, o una sal farmacéuticamente aceptable del mismo, como se menciona en cualquiera de las reivindicaciones 1 a 4, 8 a 10, o de preferencia 5 a 7 u 11 a 14, y cuando menos un material de vehículo farmacéuticamente aceptable.

20. Un método de tratamiento de una enfermedad que

dependa de la actividad de la renina, el cual comprende administrar a un animal de sangre caliente, en especial a un ser humano, que necesite dicho tratamiento, una cantidad farmacéuticamente efectiva de un compuesto de la Fórmula I, o una sal farmacéuticamente aceptable del mismo, como se menciona en cualquiera de las reivindicaciones 1 a 14 ó 15 ó 16 ó 18.

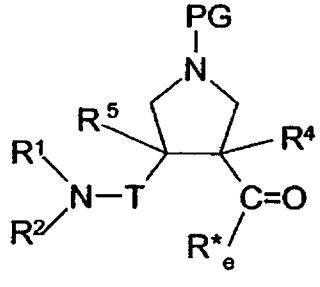
21. Un proceso para la fabricación de un compuesto de la Fórmula I, o una sal farmacéuticamente aceptable del mismo, de acuerdo con la reivindicación 4, el cual comprende:

(A) para la síntesis de un compuesto de la Fórmula I, en donde R^3 es una fracción de la Fórmula (a):



(a)

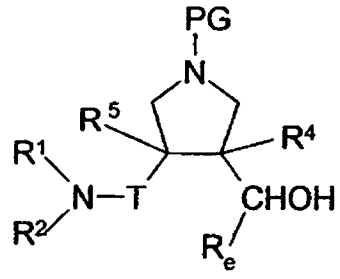
en donde R_a y R_e son como se definen para un compuesto de la Fórmula I, y R^1, R^2, R^4, R^5, y T son como se definen para un compuesto de la Fórmula I, reducir un compuesto de la Fórmula II:



(II)

en donde R^1, R^2, R^4, R^5, y T son como justamente se definieron, R^*_e es hidroxi o hidroxi eterificado, tal como OMe, o R_e

es como se define para un compuesto de la Fórmula I, y PG es un grupo protector, hasta el compuesto de hidroxi correspondiente de la Fórmula III:



(III)

en donde R_e es como se define para un compuesto de la Fórmula I, y las otras fracciones son como se definen, el cual entonces se desprotege hasta un compuesto correspondiente de la Fórmula I, en donde R_a en la fracción de la Fórmula (a) es hidrógeno, o se hace reaccionar adicionalmente con cualquiera de:

(i) con un compuesto de la Fórmula IV:

$$R_a^*\text{-}X \qquad \text{(IV)}$$

en donde R_a^* es alquilo insustituido o sustituido, arilo mono- o bi-cíclico insustituido o sustituido, hetero-ciclilo mono- o bi-cíclico insustituido o sustituido, ciclo-alquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo insustituido o sustituido, o acilo, y X es un grupo saliente, o

(ii) con el objeto de introducir una fracción R_a que es N-(arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-

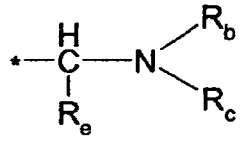
cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, o alquilo insustituido o sustituido)-amino-carbonilo, con un compuesto de isocianato de la Fórmula IV* o un clorocarbamato de la Fórmula $(R_a{**})_2$-N-C(=O)-Cl,

$$R_a{**}\text{-}N{=}C{=}O \qquad (IV^*)$$

en donde $R_a{**}$ es arilo mono- o bi-cíclico insustituido o sustituido, heterociclilo mono- o bi-cíclico insustituido o sustituido, cicloalquilo mono- o bi-cíclico insustituido o sustituido, arilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, heterociclilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, cicloalquilo mono- o bi-cíclico-alquilo de 1 a 7 átomos de carbono insustituido o sustituido, o alquilo insustituido o sustituido,

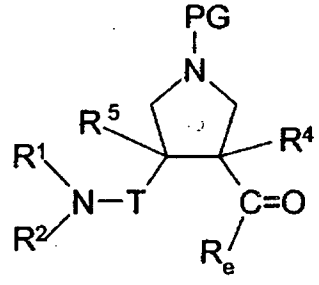
en donde la reacción (i) ó (ii) es seguida por la remoción de cualesquiera grupos protectores, para dar un compuesto correspondiente de la Fórmula I si no se desea una conversión adicional que requiera de la presencia de grupos protectores; o

(B) para la síntesis de un compuesto de la Fórmula I, en donde R^3 es una fracción de la Fórmula (b):



(b)

en donde R_e, R_b, y R_c son como se definen para un compuesto de la Fórmula I, y en donde R^1, R^2, R^4, R^5, y T son como se definen para un compuesto de la Fórmula I, hacer reaccionar un compuesto de aldehído de la Fórmula V:



(V)

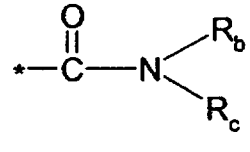
en donde R_e, R^1, R^2, R^4, R^5, y T son como se definen para un compuesto de la Fórmula I, y PG es un grupo protector,

bajo condiciones de aminación reductiva, con un compuesto de la Fórmula VI:

$$R_b\text{-}NH\text{-}R_c \qquad \text{(VI)}$$

en donde R_b y R_c son como se definen para un compuesto de la Fórmula I, seguido por, si no se pretende una conversión adicional que requiera de grupos protectores, la remoción de cualesquiera grupos protectores; o

(C) para la síntesis de un compuesto de la Fórmula I, en donde R^3 es una fracción de la Fórmula (f):

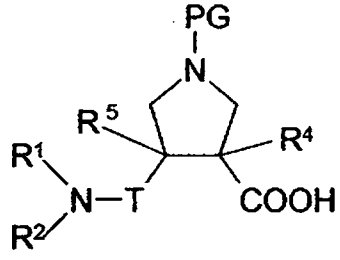


(f)

en donde R_b y R_c, así como R^1, R^2, R^4, R^5, y T son como se

definen para un compuesto de la Fórmula I,

condensar un ácido de la Fórmula IIB:



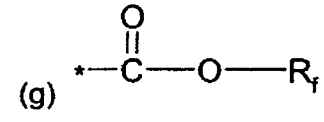
(IIB)

en donde R^1, R^2, R^4, R^5, y T son como se definen para un compuesto de la Fórmula I, y PG es un grupo protector, o un derivado reactivo del mismo, con una amina de la Fórmula VI:

$$R_b\text{-}NH\text{-}R_c \qquad \text{(VI)}$$

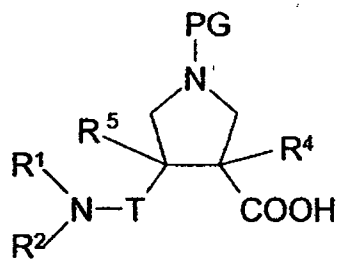
en donde R_b y R_c son como se definen para un compuesto de la Fórmula I, seguido por, si no se pretenden una conversión adicional que requiera de grupos protectores, la remoción de cualesquiera grupos protectores; o

(D) para la síntesis de un compuesto de la Fórmula I, en donde R^3 es una fracción de la Fórmula (g):



(g)

en donde R_f es como se define para un compuesto de la Fórmula I, y en donde R^1, R^2, R^4, R^5, y T son como se definen para un compuesto de la Fórmula I, hacer reaccionar un ácido de la Fórmula IIB:



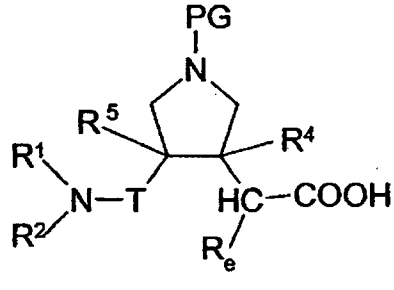
(IIB)

en donde R^1, R^2, R^4, R^5, y T son como se definen para un compuesto de la Fórmula I, y PG es un grupo protector, o un derivado reactivo del mismo, con un alcohol o un derivado de alcohol de la Fórmula VII:

$$R_f\text{-}X \qquad \text{(VII)}$$

en donde R_f es como se define para un compuesto de la Fórmula I, y X es hidroxi o un grupo saliente, seguido por, si no se pretende una conversión adicional que requiera de grupos protectores, la remoción de cualesquiera grupos protectores; o

(E) para la síntesis de un compuesto de la Fórmula I, en donde R^3 es una fracción de la Fórmula (d) ó (e) como se define para un compuesto de la Fórmula I, y R^1, R^2, R^4, R^5, y T son como se definen para un compuesto de la Fórmula I, hacer reaccionar un compuesto de la Fórmula IIA:



(IIA)

430

en donde R^1, R^2, R^4, R^5, T, y R_e son como se definen para un compuesto de la Fórmula I,

(i) para la síntesis de un compuesto de la Fórmula I, en donde R^3 es una fracción de la Fórmula (d), con un compuesto de la Fórmula VI:

$$R_b\text{-}NH\text{-}R_c \qquad (VI)$$

en donde R_a y R_b son como se definen para un compuesto de la Fórmula I, o

(ii) para la síntesis de un compuesto de la Fórmula I, en donde R^3 es una fracción de la Fórmula (e), con un compuesto de la Fórmula VII:

$$R_f\text{-}X \qquad (VII)$$

en donde R_f es como se define para un compuesto de la Fórmula I, y X es hidroxi o un grupo saliente;

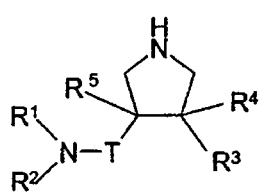
y, si se desea, subsecuentemente a cualquiera o más de los procesos (A), (B), (C), (D), o (E) mencionados anteriormente, convertir un compuesto que se pueda obtener de la Fórmula I, o una forma protegida del mismo, en un compuesto diferente de la Fórmula I, convertir una sal de un compuesto que se pueda obtener de la Fórmula I en el compuesto libre o en una sal diferente, convertir un compuesto libre que se pueda obtener de la Fórmula I en una sal del mismo, y/o separar una mezcla que se

pueda obtener de isómeros de un compuesto de la Fórmula I, en los isómeros individuales;

en donde, en cualquiera de los materiales de inicio (en especial de las fórmulas II a VII), en adición a los grupos protectores específicos mencionados, puede haber grupos protectores adicionales presentes, y cualquier grupo protector se retira en una etapa apropiada con el objeto de obtener un compuesto correspondiente de la Fórmula I, o una sal del mismo.

RESUMEN

La invención se refiere al uso de compuestos de pirrolidina (3,4-di-, 3,3,4-tri-, 3,4,4-tri-, ó 3,3,4,4-tetra-)-sustituidos, para la preparación de una formulación farmacéutica para el tratamiento de una enfermedad que dependa de la actividad de la renina; al uso de un compuesto de esta clase en el tratamiento de una enfermedad que dependa de la actividad de la renina; a compuestos que son parte de una sub-clase de estos compuestos de pirrolidina sustituida para utilizarse en el diagnóstico y en el tratamiento terapéutico de una animal de sangre caliente, en especial para el tratamiento de una enfermedad (= trastorno) que dependa de la actividad de la renina; a nuevos compuestos que son parte de una sub-clase de estos compuestos de pirrolidina sustituida; a formulaciones farmacéuticas que comprenden a estos compuestos de pirrolidina sustituida, y/o a un método de tratamiento que comprende administrar estos compuestos de pirrolidina sustituida, a un método para la fabricación en especial de estos nuevos compuestos de pirrolidina sustituida, así como a novedosos intermediarios, materiales de inicio, y/o pasos parciales para su síntesis. Los compuestos de pirrolidina sustituida son de la Fórmula I:



(I)

en donde R^1, R^2, R^3, R^4, R^5, y T se definen como en la especificación.

PATENT COOPERATION TREATY

A0

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

Processed by M/C
13. Juni 2007

PCT

To:

Dietel, Anja
Novartis AG
Corporate Intellectual Property
CH-4002 Basel
SUISSE

Corporate Intellectual Property
13. Juni 2007
Inv. | RF | LE | PA

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

	Date of mailing *(day/month/year)* 11.06.2007
Applicant's or agent's file reference PC/4-34192A	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2006/002578 ✓	21.03.2006 ✓	23.03.2005 ✓

Applicant
Novartis AG ✓

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 D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Hutterer, Georg Tel. +49 89 2399-8066

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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 PC/4-34192A	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2006/002578	International filing date *(day/month/year)* 21.03.2006	Priority date *(day/month/year)* 23.03.2005
International Patent Classification (IPC) or national classification and IPC INV. A61K31/4025		
Applicant Novartis AG		

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 8 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 electronic 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 report
☐	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
2006-12-19	11.06.2007
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer GOLEBIOWSKA, K Telephone No. +49 89 2399-8625

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2006/002578

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

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

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

   1-267 as originally filed

   Claims, Numbers

   1-21 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."*

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. 18 and 20 (with respect to industrial applicability)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*.

☒ no international search report has been established for the said claims Nos. 18 and 20 (with respect to industrial applicability)

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2006/002578

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	1-21
	No:	Claims	
Inventive step (IS)	Yes:	Claims	6, 13-21
	No:	Claims	1-5, 7-12
Industrial applicability (IA)	Yes:	Claims	1-17, 19, 21
	No:	Claims	18, 20

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

   and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Box No. VIII Certain observations on the international application

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

see separate sheet

1. Reference is made to the following documents:

   D1: *Angewandte Chemie International Edition* **2005**, *44*, 3140-3144.

Re Item III

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

2. Claims 18 and 20 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V.

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

3. None of the documents cited in the International Search Report suggests the use of a compound of Formula I for the preparation of medicament for the treatment of a disease that "depends on activity of renin". Consequently, the subject-matter of claims 1-21 is considered to be novel (Article 33(2) PCT).

4. The present application does not meet the criteria of Article 33(1) PCT because the subject-matter of claims 1-5 and 7-12 does not involve an inventive step in the sense of Article 33(3) PCT.

   According to Rule 5.1 (v) PCT, the description of application shall set forth at least the best mode for carrying out the invention claimed that shall be done in terms of examples where appropriate. However, in the present application preparation examples are only given for the compounds where T is methylene, R^4 and R^5 are only hydrogen and the R^3 moiety is selected form the group of moieties of the formula R_a, R_b, R_c, R_f. No example is given for the compounds where R_3 is selected from R_d, R_e and R_g, where T is methylene mono-substituted by alkyl, or carbonyl or thiocarbonyl and where R^4 and R^5 are selected form unsubstituted or substituted

alkyl, hydroxy or esterified or etherified hydroxy which enable a skilled person to put the invention into practice.

Moreover, in the present application, the preparation examples are given for compounds containing only 17 different heterocycles selected form the list of 304 heterocycles claimed in dependent claim 7. All these 17 heterocycles comprise either only nitrogen, only oxygen or both nitrogen and oxygen as the ring atoms. No example is given for the other 287 claimed heterocycles containing other heteroatoms such as sulphur.

The Applicant has consequently not demonstrated that the underlying problem of the invention is solved over its whole scope and an inventive step for the subject-matter of claims 1-5 and 7-12 cannot be acknowledged.

5. The present application meet the criteria of Article 33(1) PCT because the subject-matter of claims 6 and 13-21 involves an inventive step in the sense of Article 33(3) PCT.

The problem to be solved by the subject-matter of claims may be regarded as being how to provide a compound used for the manufacture of medicament for a disease that "depends on activity of renin".

The solution provided by the Applicant is the compounds of formula as disclosed in claims 6 and 13-14.

No hints can be found in the available prior art that would prompt the skilled person to use the compound of formula I according to claims 6 and 13-14 in order to solve the underlying technical problem.

The Applicant provided 369 specific examples with variety of R^1, R^2, R^3 and R^4 substituents laying in the scope of the compound as claimed in claims 6 and 13-14.

Therefore, the subject-matter of claims 6, 13, 14 and 21 is considered inventive in the sense of Article 33(3) PCT.

Furthermore, with the telefax of 8. 01. 2007 the Applicant has provided data that 18 representative examples of compounds as claimed in claim 13 and claim 6, wherein R^3 is R_a or R_b moiety, had IC_{50}s in the range from 0.45 nM to 14 nM demonstrated in the *in vitro* renin inhibition assay.

In view of above, the subject-matter of claims 15-20 (the medical use) is considered inventive in the sense of Article 33(3) PCT with respect to the compounds of formula I as claimed in claim 13 and claim 6 only for R^3 being R_a or R_b.

6. For the assessment of the present claims 18 and 20 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 the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI
Certain documents cited

7. D1 is cited under Rules 64.3 and 70.10 PCT.

Re Item VIII
Certain observations on the international application

8. Claim 16 is unclear (Article 6 PCT) because it cannot be dependent on itself. It would appear (Rule 91) that the dependency should be on claim 15.

9. The application does not meet the requirements of Article 6 PCT because the independent claim 14 could be dependent on any of claims 5-7 or 11.

10. Furthermore, claim 21 is unclear (Article 6 PCT) as it cannot refer to the compound of the formula I according to "any one of claim 4" (not only because claim 4 is a medical use claim and not a compound claim but also because the expression "any

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one of" suggests the reference to more than one claim).

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

EPO 27.07.06

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PC/4-34192A	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/EP2006/002578	International filing date *(day/month/year)* 21/03/2006	(Earliest) Priority Date *(day/month/year)* 23/03/2005
Applicant NOVARTIS AG		

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

This international search report consists of a total of 5 sheets.

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

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

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

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

4. With regard to the **title,**
   [ ] the text is approved as submitted by the applicant
   [X] the text has been established by this Authority to read as follows:

   3,4-SUBSTITUTED PYRROLIDINE DERIVATIVES FOR THE TREATMENT OF HYPERTENSION

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/002578

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4025 A61K31/341 A61K31/351 A61K31/357 A61K31/4035
A61K31/404 A61K31/416 A61K31/422 A61K31/423 A61K31/4409
A61K31/454 A61K31/4704 A61K31/506 A61K31/5355 A61K31/5377

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	E. SPECKER ET AL.: "An old target revisited: Two new privileged skeletons and an unexpected binding mode for HIV-protease inhibitors" ANGEWANDTE CHEMIE, INTERNATIONAL EDITION, vol. 44, no. 20, 13 May 2005 (2005-05-13), pages 3140-3144, XP002388826 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim ISSN: 1433-7851 Figure 2, Scheme 2.c page 3140, column 1, paragraph 1 page 3140, column 2, paragraph 3 - page 3141, column 1, paragraph 2 page 3144, column 1, paragraphs 2,3	11,12,15
A,P	----- -/--	1-10,13, 14,16-21

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

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

Date of the actual completion of the international search	Date of mailing of the international search report
10 July 2006	27/07/2006

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	Golebiowska, K

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CN 1 583 724 A (MEDICINE BIOLOGICAL TECHNOLOGY INST., CHINESE MEDICINE ACADEMY) 23 February 2005 (2005-02-23) abstract formula III page 4, lines 9-11 scheme on page 12 page 19, lines 1-8	1-21
A	EP 0 242 789 A (DAINIPPON PHARMACEUTICAL CO., LTD) 28 October 1987 (1987-10-28) abstract Formula B page 1, line 4 - page 2, line 3 page 10, lines 6-9 page 10, line 18 - page 11, line 13 page 29; example 20	1-21
A	WO 00/51609 A (MERCK & CO., INC; BAO, JIANMING; BAKER, ROBERT, K; PARSONS, WILLIAM, H) 8 September 2000 (2000-09-08) abstract page 145, lines 6-8 page 115, lines 5-12 page 75, line 1 - page 77, line 2; compound 21	1-21
A	TAYLOR G M ET AL: "On The Ritter Reaction of Cyclic Hydroxyamines: Synthesis of Conformationally-Restricted Reduced Amide Dipeptide Isosteres" TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 37, no. 8, 19 February 1996 (1996-02-19), pages 1297-1300, XP004030131 ISSN: 0040-4039 the whole document	1-21
A	N. D. L. FISHER AND N. K. HOLLENBERG: "Is there a future for renin inhibitors?" EXPERT OPINION ON INVESTIGATIONAL DRUGS, vol. 10, no. 3, 2001, pages 417-426, XP002388827 ISSN: 1354-3784 the whole document	1-21
A	WOOD J M ET AL: "Inhibitors of renin as potential therapeutic agents" JOURNAL OF ENZYME INHIBITION 1987 UNITED KINGDOM, vol. 1, no. 3, 1987, pages 169-185, XP009068927 the whole document	1-21

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/002578

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WOOD JEANETTE M ET AL: "Structure-based design of aliskiren, a novel orally effective renin inhibitor." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS. 5 SEP 2003, vol. 308, no. 4, 5 September 2003 (2003-09-05), pages 698-705, XP002388828 ISSN: 0006-291X the whole document	1-21

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2006/002578

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CN 1583724 A	23-02-2005	NONE	
EP 0242789 A	28-10-1987	AU 7190987 A	29-10-1987
		CN 87103138 A	04-11-1987
		DD 263290 A5	28-12-1988
		DK 208787 A	26-10-1987
		FI 871788 A	26-10-1987
		HU 45520 A2	28-07-1988
		JP 2572591 B2	16-01-1997
		JP 63045261 A	26-02-1988
		NO 871727 A	26-10-1987
		PH 23326 A	14-07-1989
		PT 84749 A	01-05-1987
		SU 1588281 A3	23-08-1990
		SU 1582986 A3	30-07-1990
		SU 1588282 A3	23-08-1990
		US 4886810 A	12-12-1989
		YU 27488 A1	31-10-1988
		YU 27688 A1	31-12-1988
		YU 27788 A1	30-04-1990
		YU 73987 A1	31-08-1988
		ZA 8702874 A	12-10-1987
WO 0051609 A	08-09-2000	AU 3386400 A	21-09-2000

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

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

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

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

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2006/002578	21.03.2006	23.03.2005

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/4025 A61K31/341 A61K31/351 A61K31/357 A61K31/4035 A61K31/404 A61K31/416 A61K31/422 A61K31/423 A61K31/4409 A61K31/454 A61K31/4704 A61K31/506 A61K31/5355 A61K31/5377 A61P9/12

Applicant
NOVARTIS AG

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

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

2. **FURTHER ACTION**

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

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

For further options, see Form PCT/ISA/220.

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

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Golebiowska, K Telephone No. +49 89 2399-8625

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2006/002578

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

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

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

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

1. Statement

Novelty (N)	Yes:	Claims	1-21
	No:	Claims	
Inventive step (IS)	Yes:	Claims	14
	No:	Claims	1-13, 15-21
Industrial applicability (IA)	Yes:	Claims	1-21
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Re Item V.

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

1. Reference is made to the following documents:

D1: E. Specker *et al.*, "An old target revisited: Two new privileged skeletons and an unexpected binding mode for HIV-protease inhibitors", *Angewandte Chemie, International Edition* **2005**, *44*, 3140-3144.

2. Claim 16 is unclear (Article 6 PCT) because it cannot be dependent on itself. It would appear (Rule 91) that the dependency should be on claim 15.

3. The application does not meet the requirements of Article 6 PCT because the independent claim 14 could be dependent on any of claims 5-7, 11 or 14.

4. The subject-matter of claims 1-21 is not specifically disclosed by the prior art. These claims are consequently considered to be novel (Article 33(2) PCT).

5. The present application does not meet the criteria of Article 5 and 33(1) PCT because the subject-matter of claim 1 does not involve an inventive step in the sense of Article 33(3) PCT.

The problem to be solved may be regarded as to provide a medicament for a disease that "depends on activity of renin".

The solution provided by the Applicant is the use of compounds of formula I.

None of the documents cited in the search report suggests the use of a compound of Formula I for the preparation of medicament for the treatment of a disease that "depends on activity of renin".

Although the Applicant has indicated desirable properties of the claimed compounds in the description (page 96, lines 23-24, page 97, lines 1-2, 11-12, Example 372) it has not been

shown that any single compound falling within the scope of the claims actually fulfils theses requirements. Infact, the Applicant has not shown one single example which demonstrates that the underlying problem has been solved. Thus, there are no data to demonstrate that a disease that "depends on activity of renin" is successfully treated using the compound claimed.

The subject-matter of claim 1 is hence not considered inventive in the sense of Article 33(3) PCT.

Claims 2-4, 7-10 and 15-20 do not involve an inventive step in the sense of Article 33(3) PCT for the same reasons as mentioned above.

6. In addition, the subject-matter of claims 1-3, 5, 7-11, 13 and 15-21 does not meet the requirements of Articles 5 and 33(3) PCT for the following reasons.

According to the Rule 5.1 (v) PCT, the description of application shall set forth at least the best mode for carrying out the invention claimed that shall be done in terms of examples where appropriate. However, in the present application preparation examples are only given for the compounds where T is methylene, R^4 and R^5 are only hydrogen and the R^3 moiety is selected form the group of moieties of the formula R_a, R_b, R_c, R_f. No example is given for the compounds where R_3 is selected from R_d, R_e and R_g, where T is methylene mono-substituted by alkyl, or carbonyl or thiocarbonyl and where R^4 and R^5 are selected form unsubstituted or substituted alkyl, hydroxy or esterified or etherified hydroxy.

Moreover, in the present application, the preparation examples are given for compounds containing only 17 different heterocycles selected form the list of 304 heterocycles claimed in dependent claim 7. All these 17 heterocycles comprise either only nitrogen, only oxygen or both nitrogen and oxygen as the ring atoms. No example is given for the other 287 claimed heterocycles containing other heteroatoms such as sulphur.

The Applicant has consequently not demonstrated that the underlying problem of the invention is solved over its whole scope and an inventive step cannot be acknowledged.

The subject-matter of claims 4, 6 and 12 do not involve an inventive step (Article 33(3)

PCT) for the same reasons as above, even though the subject-matter of these claim is restricted to the formula I where R^3 moiety is selected only from the group of moieties of the formula R_a, R_b, R_c, R_f. No example is given for the compounds where T is methylene mono-substituted by alkyl, or is carbonyl or thiocarbonyl and where R4 and R5 are selected form unsubstituted or substitued alkyl, hydroxy or esterified or etherified hydroxy which enable a skilled person to put the invention into practice.

7. The subject-matter of claim 14 would appear to be inventive in the sense of Article 33(3) PCT.

The problem to be solved may be regarded as to provide a compound used for the manufacture of medicament for a disease that "depends on activity of renin".

The solution provided by the Applicant is the compounds of formula as discolsed in claim 14 .

None of the documents cited in the search report suggests the use of these compounds for the manufacture of medicament for a disease that "depends on activity of renin".

It would not be obvious for the skilled person how to provide these compounds. Therefore, the subject-matter is considered inventive in the sense of Article 33(3) PCT, but only for the compound of Formula I sufficiently disclosed in the present application (See comments, point X in the present communication).

8. The Applicant's attention is furthermore drawn to the fact that in some patent systems (e.g. EPO) a simple verbal statement in a patent specification that compound X may be used to treat disease Y is not enough to ensure sufficiency of disclosure in relation to a claim to a pharmaceutical. Instead, the application must provide some information in the form of, for example, experimental tests, to the avail that the claimed compound has a direct effect on. Moreover, sufficiency of disclosure must, in principle, be shown to exist at the effective date of a patent. If the description of the patent specification provides no more than a vague indication of a possible medicinal use for a chemical compound yet to be identified, later more detailed evidence cannot be used to remedy the fundamental insufficiency of disclosure of such subject-matter.

9. For the assessment of the present claim 20 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 the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI
Certain documents cited

1. D1 is cited under Rules 64.3 and 70.10 PCT.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 07-098442- -00000-0000

Fecha: 2007-09-21 16:44:04 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 963

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION [ ] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Descripción de la invención [ ]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Edgar Navarro
Firma Responsable

Fecha 21-09-07

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Folio 965

2020
Bogotá D.C.,

Doctor(a)
OLARTE GARCIA CARLOS REINALDO
Apoderado(a) y/o Representante de
NOVARTIS AG

REFERENCIA	Radicación No.	7 98442
	Solicitud internacional	PCT/EP2006/002578
	Fecha inicio fase nacional	23/10/2007
	Trámite	11
	Evento	379
	Actuación	416
	Oficio No.	4593
	Folios	1

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC, 16 NOV. 2007

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

adpa11