Industria y Comercio

SUPERINTENDENCIA

A61K 31/395
A61P 15/00
26F

PCT

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISIÓN DE NUEVAS CREACIONES

INVENTARIO

07-135475

SOLICITUD DE PATENTE DE INVENCIÓN

TULO: DERIVADOS DE BENZOFURARONA COMO MODULADORES NO STEROIDES DE RECEPTORES DE PROGESTERONA

SOLICITANTE: BAYER SCHERING PHARMA AKTIENGESELLSCHAFT

DIRECCIÓN: Müllerstrasse 178, 13353, Berlin, Alemania.

APODERADO: J. IAN RAISBECK

BOGOTÁ 21 de Diciembre de 2007

P2007/000220

OlarteRais

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 07-135475- -00000-0000
Fecha: 2007-12-21 17:25:19 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 430

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL **P2007/000220**

SOLICITUD DE:

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

[ ] Capítulo I. [X] Capítulo II.

2. **SOLICITANTE (71)**

Nombre: BAYER SCHERING PHARMA AKTIENGESELLSCHAFT
Dirección: Müllerstrasse 178, 13353, Berlin Alemania
Nacionalidad o Domicilio: ALEMANA
Lugar de Constitución: ALEMANIA
Teléfono: _____ Fax: _____
E-mail: _____

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

3. **REPRESENTANTE O APODERADO**

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

IDENTIFICACIÓN
C.C. [x] NIT [ ]
C.E. [ ] Otro [ ]
Cual _____
Número 79.376.996 Btá
TP 135.799

4. **INVENTOR (ES) (72)**

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

5. **PCT (86)**
Solicitud Internacional No. PCT/EP2006/006532 Fecha Junio 22, 2006
Publicación Internacional No. WO/2006/136462 Fecha Diciembre 28, 2006

6. **Título (54):** DERIVADOS DE BENZOFURARONA COMO MODULADORES NO ESTEROIDES DE RECEPTORES DE PROGESTERONA

7. **Clasificación Internacional (51)** C07D 307/83, C07D 307/94, C07D 407/12, A61K 31/335, A61P 15/00, A61P 35/00.

8. **Prioridad**
SI [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
DE	Junio 24, 2005	10 2005 030 294.7

9. **Comprobante de pago No.** 07-103.652 **Fecha** Diciembre 20 de 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. 07-023402
[ ]	Documento de cesión del inventor al solicitante o a su causante.
[ ]	Declaraciones.
[x]	Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
[x]	Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
[ ]	Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
[ ]	Traducción del examen preliminar internacional efectuado por la IPEA.
[ ]	De ser el caso, copia del contrato de acceso.
[ ]	De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
[ ]	De ser el caso, certificado de 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.
[x]	De ser el caso, modificaciones efectuadas a la solicitud internacional.
[x]	Otros. Búsqueda Internacional

(12) Solicito la concesión de la patente,

NOMBRE: J. IAN RAISBECK FIRMA:

C.C. 79.376.996 Btá T.P. 135.799

3

WOLFGANG SCHWEDE,
Magdeburger Strasse 41a,
16548 Glienicke
Alemania
Nacionalidad: Alemana

CARSTEN MOELLER,
Windscheidstrasse 22,
10627 Berlin
Alemania
Nacionalidad: Alemana

ANJA SCHMIDT,
Wielandstrasse 11,
10529 Berlin
Alemania
Nacionalidad: Alemana

ULRIKE FUHRMANN,
Charlottenburger Ufer 4,
10587 Berlin
Alemania
Nacionalidad: Alemana

NORBERT SCHMEES,
Bondickstrasse 61,
13469 Berlin
Alemania
Nacionalidad: Alemana

ULRICH BOTHE,
Bredowstrasse 24,
10551 Berlin
Alemania
Nacionalidad: Alemana

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-7

RECIBO OFICIAL DE CAJA : 07 - 103,652
FECHA : DICIEMBRE 20 DE 2007

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 07-135475- -00000-0000

Fecha: 2007-12-21 17:25:19 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 379 FASENACIONALII
Act: 411 PRESENTACION Folios: 430

***** 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	57708164	17/12/2007	50,000.00
OLARTE RAISBEK	CONSIGNACION	BANCO POPULAR	050-00110-6	57708167	17/12/2007	1,949,500.00
OLARTE RAISBEK	CONSIGNACION	BANCO POPULAR	050-00110-6	57708170	17/12/2007	256,000.00
OLARTE RAISBEK	CONSIGNACION	BANCO POPULAR	050-00110-6	68286669	19/12/2007	1,324,000.00
OLARTE RAISBEK	CONSIGNACION	BANCO POPULAR	050-00110-6	71422838	20/12/2007	132,000.00

***** 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 : _____

CECBA - LEY404 GCBA
LEGALIZACION
07031211 7346
12/03/2007 13:51:46 $20.00

CECBA - LEY404 GCBA
APOSTILLE
07031 0547 13
12/03/2007 13:51:54 $39.00

FOLIO 85.- PRIMERA COPIA.- ESCRITURA NÚMERO: VEINTICUATRO.- SUSTITUCIÓN PARCIAL DE PODER: MESSERER, Dagmar a favor de OLARTE, Carlos Reinaldo y otro del Poder otorgado por BAYER SCHERING PHARMA AG.- En la Ciudad Autónoma de Buenos Aires, Capital de la República Argentina, el día **NUEVE** de **MARZO** del año **DOS MIL SIETE**, ante mí María Silvina Lasarte, Escribana Autorizante, titular del Registro Notarial número 1788, **COMPARECE: Dagmar MESSERER**, argentina, nacida el 28 de mayo de 1.968, hija de Walter Messerer y Elsa Onelia Romanelli, soltera, titular del Documento Nacional de Identidad Número 20.383.892, Clave Única de Identificación Tributaria 27-20383892-7, con domicilio especial en la Avenida Leandro N. Alem 1.134, Piso 10º, de esta Ciudad de Buenos Aires.- La compareciente es mayor de edad.- **INTERVIENE**: por su propio derecho.- Y la compareciente **EXPRESA**: **PRIMERO**: Que la Sociedad **"BAYER SCHERING PHARMA AG"**, con domicilio en Müllerstrasse 178, 13353, Berlín, Alemania, le confirió con fecha 22 de enero de 2007 en dicho país, un Poder, el cual mediante escritura número 14 de fecha 16 de febrero de 2007, otorgada ante la Escribana Mariela Vanina Scardaccione, al folio 44, protocolo corriente de este Registro Notarial interinamente a su cargo, fue incorporado y transcripto al mismo, cuya primera copia tengo para este acto a la vista, doy fe y en lo pertinente transcribiré en la presente.- **SEGUNDO**: Manifiesta bajo juramento que el referido poder se encuentra plenamente vigente en virtud de no haberle sido revocado, suspendido ni limitado en ninguna de sus partes.- **TERCERO**: En consecuencia, **DICE**: Que en uso de la facultad conferida **SUSTITUYE PARCIALMENTE** el poder mencionado a favor de **Carlos Reinaldo OLARTE y/o James Ian RAISBECK**, al solo y único objeto de que en nombre y representación de la Sociedad **"BAYER SCHERING PHARMA AG"**, y actuando en forma individual, indistinta y/o alterna-

N 007422051

damente, se presente exclusivamente ante las autoridades de **COLOMBIA** que correspondan y realicen los actos enumerados en el citado poder y con las facultades que surgen del mismo, el que transcripto en lo pertinente dice: "FOLIO 44.- PRIMERA COPIA.- ESCRITURA NÚMERO: CATORCE.- ....- En la Ciudad Autónoma de Buenos Aires, Capital de la República Argentina, el día DIECISÉIS de FEBRERO del año DOS MIL SIETE, ante mí ..., Escribana Autorizante, ..., COMPARECE: Dagmar MESSERER, argentina, nacida el 28 de mayo de 1.968, hija de Walter Messerer y Elsa Onelia Romanelli, soltera, titular del Documento Nacional de Identidad Número 20.383.892, Clave Única de Identificación Tributaria 27-20383892-7, domiciliada legalmente en la Avenida Leandro N. Alem 1.134, Piso 10°, de esta Ciudad de Buenos Aires.- La compareciente es mayor de edad.- INTERVIENE: por su propio derecho.- Y la compareciente EXPRESA: Que a los efectos que hubiere lugar, solicita de mí, la Autorizante, LA INCORPORACIÓN y TRANSCRIPCIÓN en este protocolo del PODER que le fuera conferido en Berlín, Alemania, el 22 de enero de 2007, por la Sociedad "BAYER SCHERING PHARMA AG", con domicilio en Müllerstrasse 178, 13353, Berlín, Alemania, sobre cuya plena vigencia responde la requirente bajo juramento.- Yo, la Autorizante, hago constar: a) Que el instrumento de poder cuya incorporación y transcripción a este protocolo solicita la compareciente, se encuentra extendido en idioma castellano, certificadas las firmas por notario en idioma alemán, debidamente legalizado en idioma alemán (Sello de Apostilla de la Convención de La Haya del 5 de octubre de 1961) y traducido en lo pertinente al idioma nacional por la Traductora Pública Laura Thieberger.- b) Que la compareciente en virtud de lo manifestado tiene interés legítimo en su requerimiento.- En consecuencia, me hace entrega en este acto del original del instrumento de poder relacionado con su respectiva traducción al idioma nacional, el que agrego a la presente y transcripto dice: "MOE-

LLER & CO. (Sigue aclaración en idioma inglés) - PODER Los abajo firmante/s BAYER SCHERING PHARMA AG domiciliados en Müllerstrasse 178 13353 Berlín - Alemania declaran por el presente otorgar a Dagmar MESSERER poder general amplio y suficiente para recabar de las autoridades ..., sud y centroamericanas ... que correspondan, la obtención de patentes de invención, el registro y la renovación de marcas nodelos y/o derechos de propiedad intelectual y/o nombres de dominio, a cuyo efecto los faculta/n para llevar a cabo ante dichas autoridades todas las gestiones necesarias al objeto indicado, presentar solicitudes, formular descripciones, oposiciones, protestos, declaraciones, apelaciones y reclamos, oblar impuestos, justificar explotaciones, solicitar testimonios, aceptar transferencias, recibir documentos y valores, percibir y hacer cuanto fuere necesario ante las autoridades administrativas de cualquier orden. Por otra parte, les confieren mandato para que en su nombre y representación puedan iniciar y proseguir cualquier juicio que actualmente los que suscriben tengan o er futuro tuvieran ..., en Sudamérica, Centroamérica ..., con motivo de su nombre, marcas de fábrica o de comercio, patentes de invención y modelos y/o de sus derechos de propiedad intelectual que actualmente posean o adquieran en lo sucesivo, promover juicios de cualquier jurisdicción, criminales, correccionales, civiles o comerciales, contra los falsificadores, usurpadores o imitadores y contra los tenedores de artículos que infrinjan su nombre, marcas o patentes de invención, seguir los juicios por oposición u otros en que fueran parte como actores o demandados, defender el nombre, las marcas, patentes y modelos y/o de derechos de propiedad intelectual y/o nombres de dominio, haciendo las protestas del caso o diciendo de nulidad. Al efecto, podrán presentarse con escritos, querellas, pedidos, y lo que fuere necesario ante cualquier autoridad judicial, presentar testigos, documentos y demás justificativos, rendir pruebas de cualquier especie, pedir nombramientos de peritos, pedir y absolver posiciones, asistir

a juicios verbales, declinar y prorrogar de jurisdicción, tachar, recusar, apelar, transar, someter a arbitraje o mediación, hacer renuncias, exigir y dar cauciones, pedir embargos preventivos, definitivos o inhibiciones y su levantamiento, pedir la venta de los bienes de los deudores, solicitar y obtener el cumplimiento de sentencias, prestar juramentos, decir de nulidad, desistir, percibir, otorgar recibos y en general practicar todos los actos y diligencias que sean precisos al desempeño de este mandato. Podrán asimismo substituir el presente poder en todo o en parte.- Dado y firmado en Berlín (Sigue fecha en idioma inglés). Bayer Schering Pharma AG (Sigue texto en idioma inglés). ppa. Sigue una firma ilegible. (Aclarado:) Dr. Noeske-Jungblut. ppa. Sigue otra firma ilegible. (Aclarado:) Dr. Klose". ES COPIA FIEL, doy fe.- En hoja adjunta consta la certificación notarial de las firmas obrantes en el poder en idioma alemán, efectuada el 22 de enero de 2007 por el Escribano Dimitri Rempen, de Berlín, Alemania, y a continuación consta la respectiva legalización de la firma y sello del nombrado Notario (Sello de Apostilla de la Convención de La Haya del 5 de octubre de 1961), en idioma alemán, efectuada por el Presidente del Tribunal Regional de Berlín, Alemania.- En hojas adjuntas sigue la referida traducción al idioma nacional la que transcripta textualmente, dice: "TRADUCCIÓN PUBLICA – (Sobre papel con membrete de "MOELLER y CO" - América Latina - Agentes de la Propiedad Intelectual - figura un Poder otorgado por la Sociedad "BAYER SCHERING PHARMA AG", con sede en Berlín, Alemania, redactado en idioma nacional, luego del que aparecen los siguientes textos, que traducidos dicen:) "BAYER SCHERING PHARMA AG" – Patentes y licencias – (Firmado y Aclarado:) pp Dr. Noeske-Jungblut – pp (Firmado y Aclarado:) Dr. Klose.- La versión en inglés es para su información únicamente.- Registro de Actas Nº R 17/2007.- Me he referido a la prohibición de intervención según el artículo 3, párrafo 1, Nº 7, de la Ley de Certificaciones. Mi pregunta de si ha existi-

do una intervención previa en el sentido de la norma me fue contestada por la negativa.- Las firmas trazadas ante mi por el Dr. Walter Klose, que nació el 26 de diciembre de 1952, y de la Dra. Chistiane Noeske-Jungblut de soltera Noeske, que nació el 26 de junio de 1957 – Ambos de mi personal conocimiento – Ambos con domicilio comercial en 13353 Berlín, Müllerstrasse 178 son auténticas, de lo que doy fe.- Al mismo ti[illegible]o certifico en base a que tuve a la vista en el día de hoy las actas del Registro de Comercio del Tribunal de Primera Instancia de Charlottenburg, Nº de Registro HR B 283, que la Sociedad "Bayer Schering Pharma Aktiengesellschaft", con sede en Berlín, está inscripta con el número mencionado arriba en el Registro de Comercio y que la arriba mencionada Dra. Noeske-Jungblut y el arriba mencionado Dr. Walter Klose están facultados en su carácter de mandatarios a representar en forma conjunta a la Sociedad "Bayer Schering Pharma Aktiengesellschaft" de Berlín. Berlín, 22 de enero de 2007.- El escribano (firma ilegible) y liquidación de derechos. (Hay un sello en [illegible]a sobre precinto:) Dimitri Rempen, Escribano de Berlín.- 9101ª E-F.- APOSTILLA – (Convención de La Haya del 5 de Octubre de 1961) - País: República Federal de Alemania - Este instrumento público fue firmado por Dimitri Rempen, actuando en su carácter de escribano de Berlín, estando provisto del sello del escribano.- Certificado en Berlín, el 24 de enero de 2007, por el Presidente del Tribunal Regional de Berlín, con el Nº 9101 a E-F 536/07 - Sello (hay un sello:) el Presidente del Tribunal Regional de Berlín – Firma el Funcionario autorizado (firmado y aclarado:) Holldorf – Juez Principal del Tribunal Regional.- ES TRADUCCIÓN FIEL de las partes pertinentes en los idiomas alemán e inglés del documento que se acompaña, que he vertido al idioma nacional, en Buenos Aires, a 6 de febrero de 2007.- Hay una firma ilegible. Hay un sello que dice: "LAURA THIEBERGER – MATRÍCULA DE TRADUCTORES ALEMÁN – FRANCÉS – Tomo II Folio 254 (Cap.) Tomo III – 98 – (La Plata) –

N 007422053

INGLÉS – Tomo III: Folio 14 (Cap.) – Tomo III Folio 329 (La Plata) – COLEGIO DE TRADUCTORES PÚBLICOS Nº 173".- ES COPIA FIEL, doy fe.- A continuación hay un sello que dice: "COLEGIO DE TRADUCTORES PÚBLICOS DE LA CIUDAD DE BUENOS AIRES Corresponde a la Legalización Nº T4-3278/07. Sigue una firma ilegible: Esteban Santiago Allegretti".- ES COPIA FIEL, doy fe.- Al dorso en el margen superior hay un sello timbrador ...".- A continuación sigue la legalización de la firma de la nombrada traductora, ...".- ES COPIA FIEL, doy fe.- En este estado la compareciente DICE: que en la forma expresada deja INCORPORADO y TRANSCRIPTO en este Protocolo el Poder que agrego a la presente, solicitando de mí, la Escribana Autorizante, expida primera copia de la presente para la nombrada apoderada Dagmar MESSERER.- Constancias Notariales: Identidad de la compareciente (Artículo 1.002 del Código Civil): Se justifica la misma por conocimiento de la Autorizante.- ...- LEO esta escritura a la compareciente, quien así la otorga y en prueba de conformidad, la firma ante mí, doy fe.- Dagmar MESSERER. Ante mí: MARIELA VANINA SCARDACCIONE. Escribana. Está mi sello. CONCUERDA con su escritura matriz que pasó ante mí, al folio 44 del Registro Notarial número 1788, interinamente a mi cargo.- PARA LA APODERADA expido la presente PRIMERA COPIA en tres (3) sellos de actuación notarial numerados correlativamente desde el número N 007376153 al presente inclusive, que sello y firmo en la fecha y lugar de su otorgamiento, doy fe.- Sigue una firma ilegible y un sello que dice: Mariela V. Scardaccione – Escribana – Mat. 4527.".- **ES COPIA FIEL**, de las partes pertinentes de la escritura de referencia, doy fe.- **CUARTO**: Finalmente la compareciente expresa: a) Que el presente otorgamiento no significa renunciar al ejercicio de las facultades sustituidas; y b) Que los nombrados apoderados sustitutos no podrán sustituir el presente poder en ninguna de sus partes.- **Constancias Notariales: Identidad de la Compare-**

ciente (Artículo 1.002 del Código Civil): Se justifica la misma por conocimiento de la Autorizante.-Yo, la Escribana Autorizante impongo y advierto a la compareciente, a tenor de lo dispuesto en el artículo 77 inciso h) de la Ley Orgánica Notarial Número 404, respecto de los alcances y consecuencias de las cláusulas contenidas en la presente escritura y del derecho de leer por sí este instrumento.- **LEO** esta escritura a la co ıreciente, quien así la otorga y en prueba de conformidad la firma ante mí, doy fe.- Dagmar MESSERER. Ante mí: MARIA SILVINA LASARTE. Escribana. Está mi sello. **CONCUERDA** con su escritura matriz que pasó ante mí, al folio 85 del Registro Notarial número 1788, a mi cargo. PARA LA PODERDANTE expido la presente **PRIMERA COPIA** en cuatro (4) sellos de actuación notarial numerados correlativamente desde el número N 007422051 al presente inclusive, que sello y firmo en la fecha y lugar de su otorgamiento, doy fe.-

ESCRIBANA
MARIA SILVINA
LASARTE




COLEGIO DE ESCRIBANOS
CIUDAD DE BUENOS AIRES
CAPITAL FEDERAL - REPUBLICA ARGENTINA

N 007422054

COLEGIO DE ESCRIBANOS · CIUDAD DE BUENOS AIRES · CAPITAL FEDERAL - REPUBLICA ARGENTINA

LEGALIZACION

L 007495419

EL COLEGIO DE ESCRIBANOS de la Ciudad de Buenos Aires, Capital Federal de la República Argentina, en virtud de las facultades que le confiere la ley vigente, LEGALIZA la firma y sello del escribano MARIA SILVINA LASARTE **obrantes en el documento anexo, presentado en el día de la fecha bajo el N°** 070312117346/0 **La presente legalización no juzga sobre el contenido y forma del documento.**

Buenos Aires, Lunes 12 de Marzo de 2007

COLEGIO DE ESCRIBANOS · LEGALIZACION · CIUDAD DE BUENOS AIRES · CAPITAL FEDERAL - REPUBLICA ARGENTINA

ESC. EDDA ENRIQUETA SINELLI
COLEGIO DE ESCRIBANOS
CONSEJERA

CONSEJERO

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

A 00115229

1. PAÍS: REPUBLICA ARGENTINA

El presente documento público

2. Ha sido firmado por EDDA ENRIQUETA SINELLI

3. Quien actúa en calidad de CONSEJERA

4. Lleva el sello / timbre de COLEGIO DE ESCRIBANOS DE LA CIUDAD DE BUENOS AIRES

5. En LA CIUDAD DE BUENOS AIRES 6. El día 12/03/2007

7. Por EL COLEGIO DE ESCRIBANOS DE LA CIUDAD DE BUENOS AIRES

MINISTERIO DE RELACIONES EXTERIORES, COMERCIO INTERNACIONAL Y CULTO

(Convenio 02/09/2003)

8. Bajo el número: 070312054713

9. Sello / Timbre

COLEGIO DE ESCRIBANOS APOSTILLA CAPITAL FEDERAL - REPUBLICA ARGENTINA

10. Firma

INSPECTOR GENERAL
COLEGIO DE ESCRIBANOS
CONSEJERO

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 December 2006 (28.12.2006)

PCT

(10) International Publication Number
WO 2006/136462 A1

(51) International Patent Classification:
C07D 307/83 (2006.01) *A61K 31/335* (2006.01)
C07D 307/94 (2006.01) *A61P 15/00* (2006.01)
C07D 407/12 (2006.01) *A61P 35/00* (2006.01)

(21) International Application Number:
PCT/EP2006/006532

(22) International Filing Date: 22 June 2006 (22.06.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10 2005 030 294.7 24 June 2005 (24.06.2005) DE

(71) Applicant *(for all designated States except US)*: **SCHERING AKTIENGESELLSCHAFT** [—/DE]; Müllerstrasse 178, 13353 Berlin (DE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **SCHWEDE, Wolfgang** [DE/DE]; Magdeburger Strasse 41a, 16548 Glienicke (DE). **MOELLER, Carsten** [DE/DE]; Windscheidstrasse 22, 10627 Berlin (DE). **SCHMIDT, Anja** [DE/DE]; Wielandstrasse 11, 10529 Berlin (DE). **FUHRMANN, Ulrike** [DE/DE]; Charlottenburger Ufer 4, 10587 Berlin (DE). **SCHMEES, Norbert** [DE/DE]; Bondickstrasse 61, 13469 Berlin (DE). **BOTHE, Ulrich** [DE/DE]; Bredowstrasse 24, 10551 Berlin (DE).

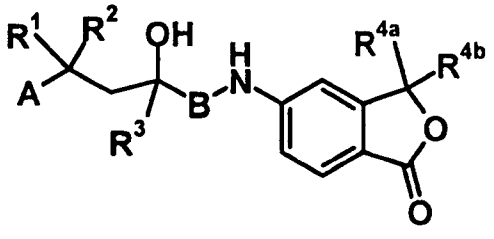
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ,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

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

Published:
— *with international search report*
— *with amended claims and statement*

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

(54) Title: BENZOFURANONE DERIVATIVES AS NONSTEROIDAL PROGESTERONE RECEPTOR MODULATORS



(I)

(57) Abstract: This invention relates to nonsteroidal progesterone receptor modulators of general formula (I), a process for their production, the use of progesterone receptor modulators for the production of pharmaceutical agents as well as pharmaceutical compositions that contain these compounds. The compounds according to the invention are suitable for therapy and prophylaxis of gynecological diseases, such as endometriosis, leiomyomas of the uterus, dysfunctional bleeding and dysmenorrhea, as well as for the therapy and prophylaxis of hormone-dependent tumors and for use for female birth control as well as for hormone replacement therapy.

WO 2006/136462 A1

BENZOFURANONE DERIVATIVES AS NONSTEROIDAL PROGESTERONE RECEPTOR MODULATORS

This invention relates to nonsteroidal progesterone receptor modulators, a process for their production, the use of progesterone receptor modulators for the production of pharmaceutical agents as well as pharmaceutical compositions that contain these compounds.

The steroid hormone progesterone regulates the reproductive process in the female organism in a decisive way. During the cycle and in pregnancy, progesterone is secreted in large amounts from the ovary or the placenta. By interaction with estrogens, progesterone produces cyclic changes of the uterine mucous membrane (endometrium) in the menstrual cycle. Under the influence of elevated progesterone levels after ovulation, the uterine mucous membrane is converted into a state that allows the nidation of an embryo (blastocyte). In pregnancy, progesterone controls the relaxation of the myometrium and retains the function of the decidual tissue.

In addition, it is known that progesterone inhibits the endometrial proliferation by the suppression of the estrogen-mediated mitosis in the uterus tissue (K. Chwalisz, R. M. Brenner, U. Fuhrmann, H. Hess-Stumpp, W. Elger, Steroids 65, 2000, 741-751).

An important role of the progesterone and the progesterone receptors is also known in pathophysiological processes. Progesterone receptors are detected in foci of endometriosis, but also in tumors of the uterus, the breast and the CNS. In addition, it is known that uterus leiomyomas grow in a progesterone-dependent manner.

The actions of progesterone in the tissues of genital organs and in other tissues are carried out by interactions with progesterone receptors, which are responsible for the cellular effects.

Progesterone receptor modulators are either pure agonists or partially or completely inhibit the action of progesterone. Consequently, substances are defined as pure agonists, partial agonists (SPRMS) and pure antagonists.

According to the ability of the progesterone receptor modulators to influence the action of the progesterone receptor, these compounds have a considerable potential as therapeutic agents for gynecological and oncological indications as well as for obstetrics and birth control.

Pure progesterone receptor antagonists completely inhibit the action of progesterone in the progesterone receptor. They have antiovulatory properties as well as the ability to inhibit estrogen effects in the endometrium up to full atrophy. They are therefore especially suitable for intervening in the female reproductive process, e.g., in post-ovulation, to prevent nidation; in pregnancy, to increase the reactivity of the uterus to prostaglandins or oxytocin or to ensure the opening and softening ("maturation") of the cervix as well as to make the myometrium highly prepared for labor.

In foci of endometriosis or in tumor tissue, which are (is) equipped with progesterone receptors, an advantageous influence of the disease process is expected after application of pure progesterone receptor antagonists. Special advantages for influencing pathologic conditions, such as endometriosis or uterus leiomyomas, could then be given if in addition an inhibition of the ovulation can be achieved by the progesterone receptor antagonists. When ovulation is inhibited, a portion of the ovarian hormone production and thus the stimulative effect that is due to this portion are also due to the pathologically altered tissue.

A large number of analogs with varying degrees of progesterone receptor-antagonistic activity followed the first described progesterone receptor antagonist RU 486 (also mifepristone). While RU 486, in addition to the progesterone receptor-

antagonistic action, also shows an antiglucocorticoidal action, compounds synthesized later are distinguished primarily by a more selective action than progesterone receptor antagonists.

From the literature, in addition to steroidal compounds such as onapristone or lilopristone, which are distinguished from progesterone-receptor-antagonistic action to antiglucorticoidal action relative to RU 486 by a better dissociation of action, various nonsteroidal structures, whose antagonistic action on the progesterone receptor is examined, are also known [see, e.g., S. A. Leonhardt and D. P. Edwards, Exp. Biol. Med. 227: 969-980 (2002) and R. Winneker, A. Fensome, J. E. Wrobel, Z. Zhang, P. Zhang, Seminars in Reproductive Medicine, Volume 23: 46-57 (2005)]. Previously known compounds, however, have only moderately antagonistic activity compared to the known steroidal structures. The most effective nonsteroidal compounds are described as having *in vitro* activities of 10% of the activity of RU 486.

The antiglucocorticoidal activity is disadvantageous for a therapeutic application in which the inhibition of the progesterone receptors is a primary focus of therapy. An antiglucocorticoidal activity causes undesirable side effects in the case of therapeutically necessary dosages. This can prevent the application of a therapeutically useful dose or lead to termination of the treatment.

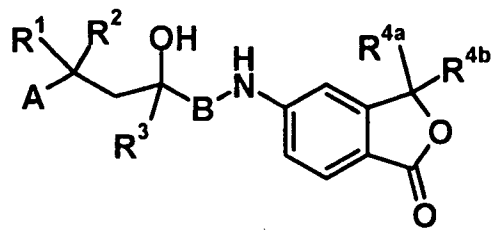
The partial or complete reduction of the antiglucocorticoidal properties is therefore an important requirement for the therapy with progesterone receptor antagonists, in particular for those indications that require a treatment lasting weeks or months.

In contrast to the pure antagonists, progesterone receptor partial agonists (SPRMs) show a residual agonistic property, which can be strongly pronounced to different degrees. This leads to the fact that these substances show potential agonistic

actions of the progesterone receptor in specific organ systems (D. DeManno, W. Elger, R. Garg, R. Lee, B. Schneider, H. Hess-Stumpp, G. Schuber, K. Chwalisz, Steroids 68, 2003, 1019-1032). Such an organ-specific and dissociated action can be of therapeutic use for the indications described.

It is therefore the object of this invention to make available additional nonsteroidal progesterone receptor modulators. These compounds are to have a reduced antiglucocorticoidal action and are therefore suitable for the therapy and prophylaxis of gynecological diseases such as endometriosis, leiomyomas of the uterus, dysfunctional bleeding and dysmenorrhea. In addition, the compounds according to the invention are to be suitable for the therapy and prophylaxis of hormone-dependent tumors, for example breast, endometrial, ovarian and prostate cancers. In addition, the compounds are to be suitable for use in female birth control and for female hormone replacement therapy.

The object is achieved according to this invention by the preparation of non-steroidal compounds of general formula I



(I),

in which

R^1 and R^2, independently of one another, mean a hydrogen atom, a straight or nonstraight, branched or unbranched C_1-C_5-alkyl group, also together with the C atom of the chain forming a ring with a total of 3-7 members,

R^3 means a radical $C\equiv C\text{-}R^a$, whereby

R^a means a hydrogen or a C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkinyl, C_3-C_{10}-cycloalkyl, or heterocycloalkyl that optionally is substituted in one or more places, in the same way or differently, with K, or an aryl or heteroaryl that optionally is substituted in one or more places, in the same way or differently, with L,

K is a cyano, halogen, hydroxy, nitro, $-C(O)R^b$, CO_2R^b, $-O-R^b$, $-S-R^b$, $SO_2NR^cR^d$, $-C(O)-NR^cR^d$, $-OC(O)-NR^cR^d$, or $-C=NOR^b$ $-NR^cR^d$ or a C_3-C_{10}-cycloalkyl that optionally is substituted in one or more places, in the same way or differently, with M, heterocycloalkyl, or aryl or heteroaryl that optionally is substituted in one or more places with L,

L means C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkinyl, C_1-C_6-perfluoroalkyl, C_1-C_6-perfluoroalkoxy, C_1-C_6-alkoxy-C_1-C_6-alkoxy, $(CH_2)_p$-C_3-C_{10}-cycloalkyl, $(CH_2)_p$-heterocycloalkyl, $(CH_2)_pCN$, $(CH_2)_pHal$, $(CH_2)_pNO_2$, $(CH_2)_p$-C_6-C_{12}-aryl, $(CH_2)_p$-heteroaryl, $-(CH_2)_pPO_3(R^b)_2$, $-(CH_2)_pNR^cR^d$, $-(CH_2)_pNR^eCOR^b$, $-(CH_2)_pNR^eCSR^b$, $-(CH_2)_pNR^eS(O)R^b$, $-(CH_2)_pNR^eS(O)_2R^b$, $-(CH_2)_pNR^eCONR^cR^d$, $-(CH_2)_pNR^eCOOR^b$, $-(CH_2)_pNR^eC(NH)NR^cR^d$, $-(CH_2)_pNR^eCSNR^cR^d$, $-(CH_2)_pNR^eS(O)NR^cR^d$, $-(CH_2)_pNR^eS(O)_2NR^cR^d$, $-(CH_2)_pCOR^b$, $-(CH_2)_pCSR^b$, $-(CH_2)_pS(O)R^b$, $-(CH_2)_pS(O)(NH)R^b$, $-(CH_2)_pS(O)_2R^b$,

$-(CH_2)_pS(O)_2NR^cR^d$, $-(CH_2)_pSO_2OR^b$, $-(CH_2)_pCO_2R^b$, $-(CH_2)_pCONR^cR^d$, $-(CH_2)_pCSNR^cR^d$, $-(CH_2)_pOR^b$, $-(CH_2)_pSR^b$, $-(CH_2)_pCR^b(OH)-R^e$, $-(CH_2)_p-C=NOR^b$, $-O-(CH_2)_n-O-$, $-O-(CH_2)_n-CH_2-$, $-O-CH=CH-$ or $-(CH_2)_{n+2}-$, whereby n = 1 or 2, and the terminal oxygen atoms and/or carbon atoms are linked to directly adjacent ring-carbon atoms,

M means C_1-C_6-alkyl or a group $-COR^b$, CO_2R^b, $-O-R^b$, or $-NR^cR^d$, whereby

R^b means a hydrogen or a C_1-C_6-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkinyl, C_3-C_{10}-cycloalkyl, C_6-C_{12}-aryl or C_1-C_3-perfluoroalkyl, and

R^c and R^d, independently of one another, mean a hydrogen, C_1-C_6-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkinyl, C_3-C_{10}-cycloalkyl, C_6-C_{12}-aryl, $C(O)R^b$ or a hydroxy group, whereby if

R^c is a hydroxy group, R^d can be only one hydrogen, a C_1-C_6-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkinyl, C_3-C_{10}-cycloalkyl or C_6-C_{12}-aryl and vice versa, and

R^e means a hydrogen, C_1-C_6-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkinyl, C_3-C_{10}-cycloalkyl or C_6-C_{12}-aryl, and

p can be a number from 0- 6,

or

R^3 is a radical C = C-R^gR^h, whereby

R^g and R^h, independently of one another, are a hydrogen or a C_1-C_8-alkyl, C_2-C_8-alkenyl or C_2-C_8-alkinyl that optionally is substituted in one or more places, in the same way or differently, with X, in which

X is a cyano, halogen, hydroxy, nitro, -C(O)R^b, CO_2R^b, –O-R^b, -C(O)-NR^cR^d, -NR^cR^d with the meanings already further mentioned above for R^b, R^c and R^d, and

R^{4a} and R^{4b}, independently of one another, mean a hydrogen atom, a C_1-C_4-alkyl, a C_2-C_4-alkenyl or together with the ring-carbon atom forming a 3- to 6-membered ring,

A means a monocyclic or bicyclic, carbocyclic or heterocyclic aromatic ring, which optionally can be substituted in one or more places with C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkinyl, C_1-C_6-perfluoroalkyl, C_1-C_6-perfluoroalkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkoxy, $(CH_2)_p$-C_3-C_{10}-cycloalkyl, $(CH_2)_p$-heterocycloalkyl, $(CH_2)_pCN$, $(CH_2)_pHal$, $(CH_2)_pNO_2$, $(CH_2)_p$-C_6-C_{12}-aryl, $(CH_2)_p$-heteroaryl, -$(CH_2)_pPO_3(R^b)_2$, -$(CH_2)_pNR^cR^d$, -$(CH_2)_pNR^eCOR^b$, -$(CH_2)_pNR^eCSR^b$, -$(CH_2)_pNR^eS(O)R^b$, -$(CH_2)_pNR^eS(O)_2R^b$, -$(CH_2)_pNR^eCONR^cR^d$, -$(CH_2)_pNR^eCOOR^b$, -$(CH_2)_pNR^eC(NH)NR^cR^d$, -$(CH_2)_pNR^eCSNR^cR^d$, -$(CH_2)_pNR^eS(O)NR^cR^d$, -$(CH_2)_pNR^eS(O)_2NR^cR^d$, -$(CH_2)_pCOR^b$, -$(CH_2)_pCSR^b$, -$(CH_2)_p$ $S(O)R^b$, -$(CH_2)_pS(O)(NH)R^b$, -$(CH_2)_pS(O)_2R^b$, -$(CH_2)_pS(O)_2NR^cR^d$, -$(CH_2)_pSO_2OR^b$, -$(CH_2)_pCO_2R^b$, -$(CH_2)_pCONR^cR^d$, -$(CH_2)_pCSNR^cR^d$, -$(CH_2)_pOR^b$, -$(CH_2)_pSR^b$, -$(CH_2)_pCR^b(OH)$-R^d, -$(CH_2)_p$-C=NOR^b, -O-$(CH_2)_n$-O-, -O-$(CH_2)_n$-CH_2-, -O-CH=CH- or

$-(CH_2)_{n+2}-$, whereby n = 1 or 2, and the terminal oxygen atoms and/or carbon atoms are linked to directly adjacent ring-carbon atoms, or

A means a radical $-CO_2R^b$, $C(O)NR^cR^d$, COR^b,

or

A means an alkenyl group $-CR^5 = CR^6R^7$, whereby

R^5, R^6 and R^7 are the same or different and, independently of one another, mean hydrogen atoms, halogen atoms, aryl radicals or an unsubstituted or partially or completely fluorinated C_1-C_5–alkyl group, or

A means an alkinyl group $-C\equiv CR^5$, with the meaning cited above for R^5, and

B means a carbonyl group or a CH_2 group

as well as their pharmaceutically acceptable salts.

The compounds of general formula I according to the invention can be present as different stereoisomers because of the presence of asymmetry centers. Both the racemates and the separately present stereoisomers are part of the subject of this invention.

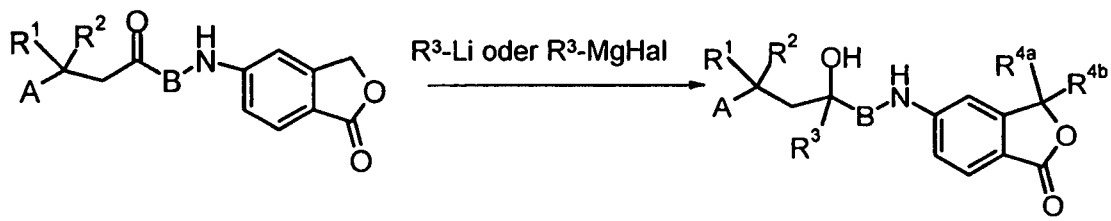
In addition, this invention comprises the new compounds as pharmaceutical active ingredients, their production, their therapeutic application and pharmaceutical dispensing forms that contain the new substances.

The compounds of general formula (I) according to the invention or their pharmaceutically acceptable salts can be used for the production of a pharmaceutical agent, especially for treatment and prophylaxis of gynecological diseases, such as endometriosis, leiomyomas of the uterus, dysfunctional bleeding and dysmenorrhea. In addition, the compounds according to the invention can be used for the treatment and

prophylaxis of hormone-dependent tumors, such as, for example, for breast, prostate and endometrial cancers.

The compounds of general formula (I) according to the invention or their pharmaceutically acceptable salts are suitable for use for female birth control or for female hormone replacement therapy.

A process for the production of the compounds of general formula (I), moreover, is also a subject of this invention. Substituent R^3 is introduced to a keto group by selective addition reaction of organometallic compounds such as lithium alkinylene or magnesium haloalkinylene. This results, either directly or after implementing additional modifications, in the compounds of general formula (I) according to the invention.



[or]

The production of the compounds according to the invention is carried out by selective addition of organometallic compounds to ketoamides, which were described in, e.g., laid-open specifications WO 200375915 and WO 9854159. The organometallic compounds can be, for example, lithium alkinyl compounds or magnesium haloalkinyl compounds. The latter are produced by, e.g., reaction of the corresponding alkines with butyllithium or Grignard compounds. Analogously to this, the corresponding

organometallic alkenyl compounds can also be produced. The reactivity of the keto group in comparison to amidocarbonyl or to phthalide is in this case significantly higher, such that with suitable selection of the reaction conditions, a selective addition is achieved. As an alternative, the alkinyl or alkenyl radicals that are introduced as R^3 can also be further modified later. For these modifications, reactions that have become known to one skilled in the art, such as oxidation, reduction, substitution, alkylation, or palladium-catalyzed reaction, are suitable. Optionally present protective groups are cleaved off at a suitable time.

The nonsteroidal compounds of general formula I according to the invention have a strongly antagonistic or strongly partially agonistic action on the progesterone receptor. They exhibit a strong dissociation of action with respect to their bonding strength on the progesterone receptor and on the glucocorticoid receptor. While known progesterone receptor antagonists, such as Mifepristone (RU 486), in addition to the desired high binding affinity for the progesterone receptor likewise show a high affinity for the glucocorticoid receptor, the compounds according to the invention are distinguished by a very low glutocorticoid receptor bond with simultaneously present high progesterone receptor affinity.

The substituents of the compounds of general formula I according to the invention that are defined as groups can have the meanings below in each case:

C_1-C_5-, C_1-C_6- or C_1-C_8-alkyl groups are defined as straight or nonstraight, branched or unbranched alkyl radicals. In this case, for example, this is a methyl, ethyl, n-propyl, iso-propyl, n-, iso-, tert-butyl, an n-pentyl, 2,2-dimethylpropyl, 3-methylbutyl, hexyl, heptyl or octyl group.

In terms of R^a, in this case, the methyl, ethyl, n-propyl or n-butyl group as well as an n-pentyl group are preferred.

In terms of R^1 and R^2, methyl or ethyl is preferred.

According to the invention, a hydrogen is preferred for $R4^a$ and $R4^b$.

Alkenyl is defined as straight or nonstraight, branched or unbranched alkenyl radicals. In terms of the invention, a C_2–C_8-alkenyl group is defined, for example, as follows: vinyl, allyl, 3-buten-1-yl- or 2,3-dimethyl-2-propenyl. If aromatic compound A is substituted with a C_2–C_8-alkenyl radical, this is preferably a vinyl group.

Alkinyl is defined as straight or nonstraight, branched or unbranched alkinyl radicals. For example, an ethinyl, propinyl, butinyl, pentinyl, hexinyl or octinyl group, but preferably an ethinyl or propinyl group, is to stand for a C_2–C_8-alkinyl radical.

For C_3-C_{10}-cycloalkyl, for example, cyclopropane, cyclobutane, cyclopentane and cyclohexane can be mentioned. Cyclopropyl, cyclopentyl and cyclohexyl are preferred.

In terms of R^a, K or L, heterocycloalkyl is defined as 3- to 8-membered heterocycloalkyl radicals. Examples of heterocycloalkyl are morpholine, tetrahydrofuran, pyran, piperazine, piperidine, pyrrolidine, oxirane, oxetane, aziridine, dioxolane and dioxane. In this case, the position of the heteroatom in relation to the point of linkage can be any chemically possible position.

For example, methoxymethoxy, ethoxymethoxy or 2-methoxyethoxy can stand for a C_1-C_6-alkoxyl-C_1-C_6-alkoxy group.

In terms of the invention, a radical OR^b is a hydroxy, methoxy, ethoxy, n-propoxy, iso-propoxy, n-, iso-, or tert-butoxy group, or an n-pentoxy, 2,2-dimethylpropoxy or 3-methylbutoxy group. Hydroxy, methoxy and ethoxy are preferred.

For a partially or completely fluorinated C_1-C_5-alkyl group, the perfluorinated alkyl groups that appear above are considered. Of the latter, primarily the

trifluoromethyl group or the pentafluoroethyl group as well as as partially fluorinated alkyl groups, for example the 5,5,4,4-pentafluoropentyl group or the 5,5,5,4,4,3,3-heptafluoropentyl group, are preferred.

A fluorine, chlorine, bromine or iodine atom can stand for a halogen atom. Preferred here is fluorine, chlorine or bromine.

If R^1 and R^2 together with the C atom of the chain form a 3- to 7-membered ring, this is, for example, a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl ring. The cyclopropyl ring as well as the cyclopentyl ring are preferred.

The monocyclic or bicyclic carbocyclic aromatic ring A, which can be substituted in several places, is a carbocyclic or heterocyclic aryl radical.

In the first case, it is, for example, a phenyl or naphthyl radical, preferably a phenyl radical.

As a heterocyclic radical, for example, a monocyclic heterocyclic radical, for example the thienyl, furyl, pyranyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, thiazolyl, oxazolyl, furazanyl, pyrrolinyl, imidazolinyl, pyrazolinyl, thiazolinyl, triazolyl, or tetrazolyl radical, and specifically all possible isomers relative to the positions of the heteroatoms, can be used.

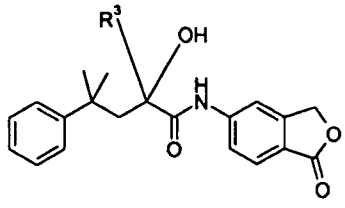
In terms of R^3, an aryl radical is an optionally substituted phenyl, 1- or 2-naphthyl radical, whereby the phenyl radical is preferred. Examples of a heteroaryl radical are the 2-, 3- or 4-pyridinyl radical, the 2- or 3-furyl radical, the 2- or 3-thienyl radical, the 2- or 3-pyrrolyl radical, the 2-, 4- or 5-imidazolyl radical, the pyrazinyl radical, the 2-, 4- or 5-pyrimidinyl radical or the 3- or 4-pyridazinyl radical.

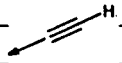
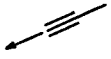
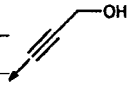
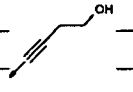
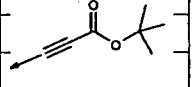
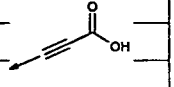
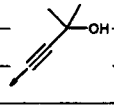
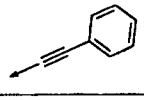
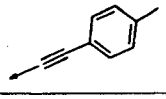
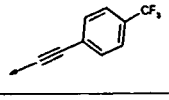
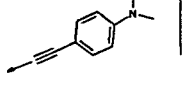
The number p for the $(CH_2)_p$ radical can be a number from 0 to 6, preferably 0 to 2. "Radicals" are defined according to the invention as all functional groups that are presented in connection with $(CH_2)_p$.

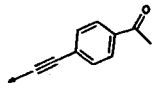
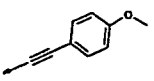
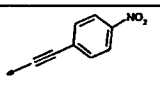
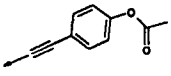
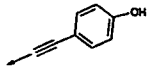
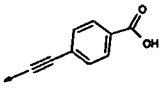
In the case that the compounds of general formula I (B = -CH_2-) are present as salts, this can be, for example, in the form of hydrochloride, sulfate, nitrate, tartrate, citrate, fumarate, succinate or benzoate.

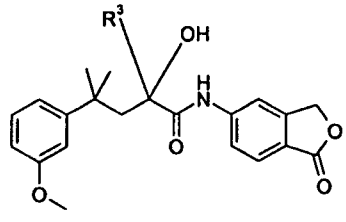
If the compounds according to the invention are present as racemic mixtures, they can be separated into the pure, optically active forms according to methods of racemate separation that are familiar to one skilled in the art. For example, the racemic mixtures can be separated into pure isomers by chromatography on an even optically active carrier material (CHIRALPAK AD®). It is also possible to esterify the free hydroxy group in a racemic compound of general formula I with an optically active acid and to separate the diastereomeric esters that are obtained by fractionated crystallization or by chromatography and to saponify the separated esters in each case to form the optically pure isomers. As an optically active acid, for example, mandelic acid, camphorsulfonic acid or tartaric acid can be used.

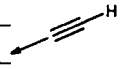
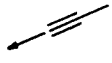
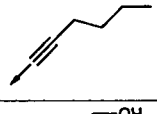
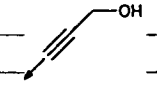
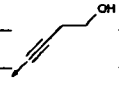
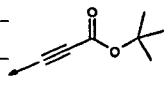
The compounds that are mentioned below as well as the use thereof are preferred according to the invention:

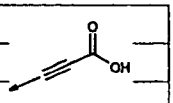
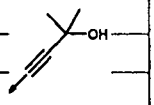
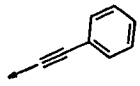
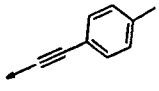
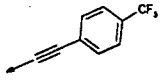
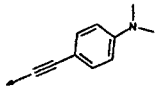
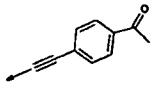
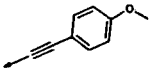
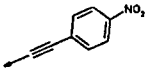
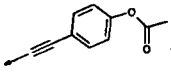
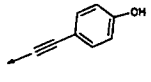
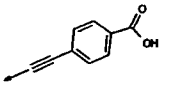


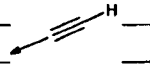
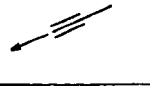
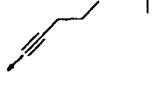
No.	Racemic or Enantiomer	R3
1	rac	
2	+	
3	-	
4	rac	
5	+	
6	-	
7	rac	
8	+	
9	-	
10	rac	
11	+	
12	-	
13	rac	
14	+	
15	-	
16	rac	
17	+	
18	-	
19	rac	
20	+	
21	-	
22	rac	
23	+	
24	-	
25	rac	
26	+	
27	-	
28	rac	
29	+	
30	-	
31	rac	
32	+	
33	-	
34	rac	
35	+	
36	-	
37	rac	
38	+	
39	-	
40	rac	
41	+	

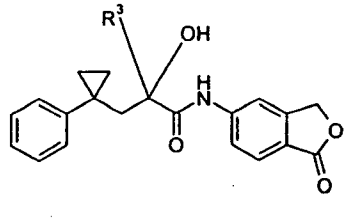
42	-	
43	rac	
44	+	
45	-	
46	rac	
47	+	
48	-	
49	rac	
50	+	
51	-	
52	rac	
53	+	
54	-	
55	rac	
56	+	
57	-	
58	rac	
59	+	
60	-	

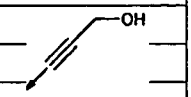
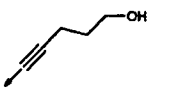
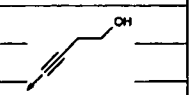
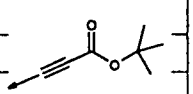
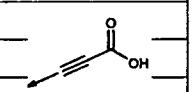
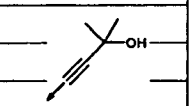
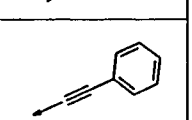
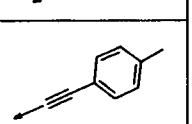
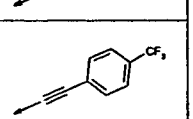
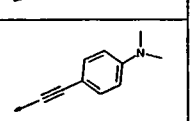
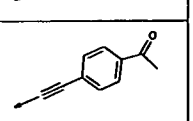
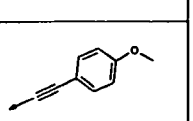
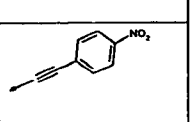
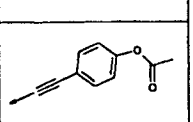


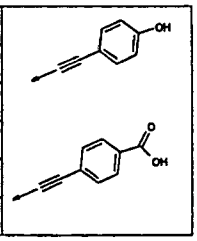
No.	Racemic or Enantiomer	R3
61	rac	
62	+	
63	-	
64	rac	
65	+	
66	-	
67	rac	
68	+	
69	-	
70	rac	
71	+	
72	-	
73	rac	
74	+	
75	-	
76	rac	
77	+	
78	-	
79	rac	
80	+	
81	-	
82	rac	
83	+	
84	-	

85	rac	
86	+	
87	-	
88	rac	
89	+	
90	-	
91	rac	
92	+	
93	-	
94	rac	
95	+	
96	-	
97	rac	
98	+	
99	-	
100	rac	
101	+	
102	-	
103	rac	
104	+	
105	-	
106	rac	
107	+	
108	-	
109	rac	
110	+	
111	-	
112	rac	
113	+	
114	-	
115	rac	
116	+	
117	-	
118	rac	
119	+	
120	-	

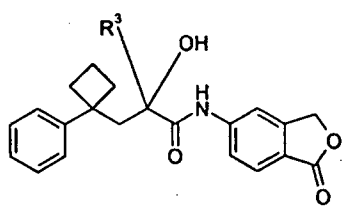
No.	Racemic or Enantiomer	R3
121	rac	
122	+	
123	-	
124	rac	
125	+	
126	-	
127	rac	

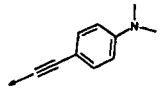
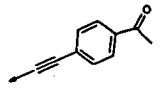
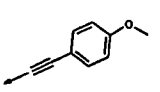
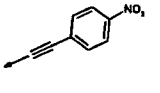
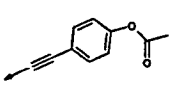
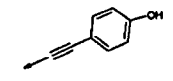
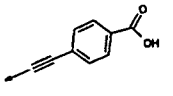


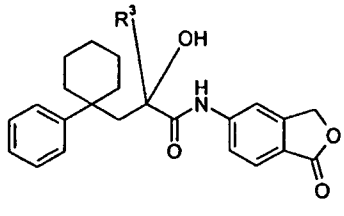
128	+	
129	-	
130	rac	
131	+	
132	-	
133	rac	
134	+	
135	-	
136	rac	
137	+	
138	-	
139	rac	
140	+	
141	-	
142	rac	
143	+	
144	-	
145	rac	
146	+	
147	-	
148	rac	
149	+	
150	-	
151	rac	
152	+	
153	-	
154	rac	
155	+	
156	-	
157	rac	
158	+	
159	-	
160	rac	
161	+	
162	-	
163	rac	
164	+	
165	-	
166	rac	
167	+	
168	-	
169	rac	
170	+	
171	-	
172	rac	
173	+	
174	-	

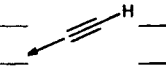
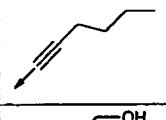
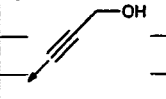
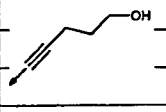
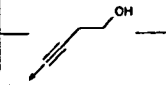
175	rac	
176	+	
177	-	
178	rac	
179	+	
180	-	

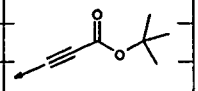
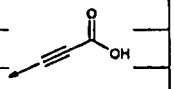
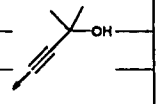
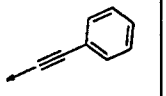
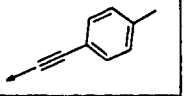
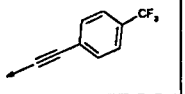
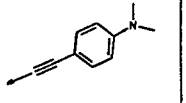
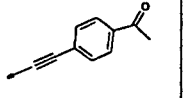
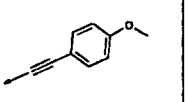
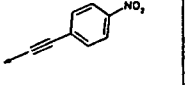
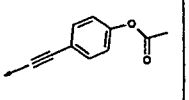
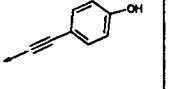
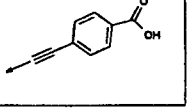


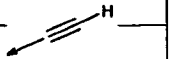
No.	Racemic or Enantiomer	R3
181	rac	
182	+	
183	-	
184	rac	
185	+	
186	-	
187	rac	
188	+	
189	-	
190	rac	
191	+	
192	-	
193	rac	
194	+	
195	-	
196	rac	
197	+	
198	-	
199	rac	
200	+	
201	-	
202	rac	
203	+	
204	-	
205	rac	
206	+	
207	-	
208	rac	
209	+	
210	-	
211	rac	
212	+	
213	-	
214	rac	
215	+	
216	-	
217	rac	
218	+	

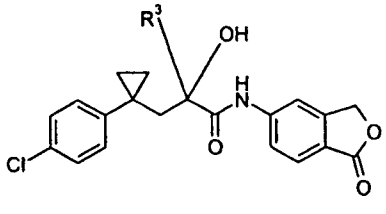
219	-	
220	rac	
221	+	
222	-	
223	rac	
224	+	
225	-	
226	rac	
227	+	
228	-	
229	rac	
230	+	
231	-	
232	rac	
233	+	
234	-	
235	rac	
236	+	
237	-	
238	rac	
239	+	
240	-	

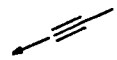
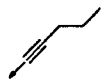
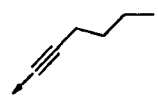
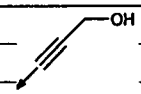
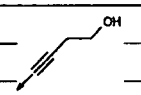
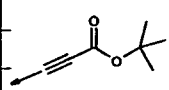
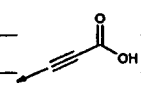
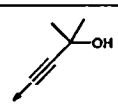
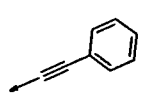
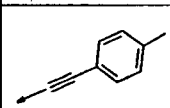
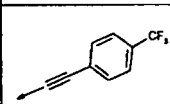
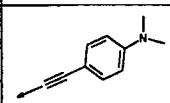
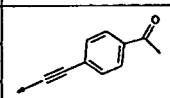
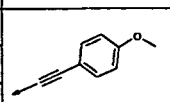
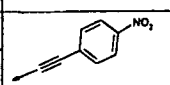


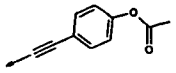
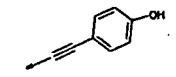
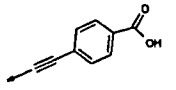
No.	Racemic or Enantiomer	R3
241	rac	
242	+	
243	-	
244	rac	
245	+	
246	-	
247	rac	
248	+	
249	-	
250	rac	
251	+	
252	-	
253	rac	
254	+	
255	-	
256	rac	
257	+	
258	-	
259	rac	
260	+	

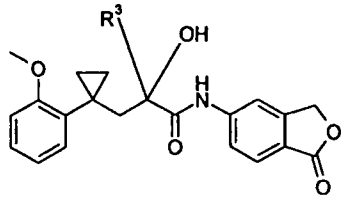
261	-	
262	rac	
263	+	
264	-	
265	rac	
266	+	
267	-	
268	rac	
269	+	
270	-	
271	rac	
272	+	
273	-	
274	rac	
275	+	
276	-	
277	rac	
278	+	
279	-	
280	rac	
281	+	
282	-	
283	rac	
284	+	
285	-	
286	rac	
287	+	
288	-	
289	rac	
290	+	
291	-	
292	rac	
293	+	
294	-	
295	rac	
296	+	
297	-	
298	rac	
299	+	
300	-	

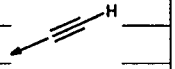
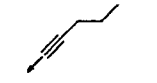
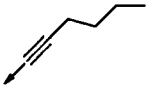
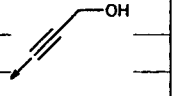
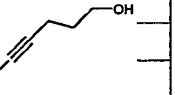
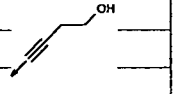
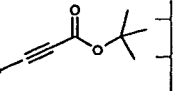
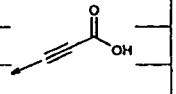
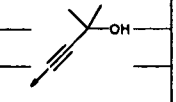
No.	Racemic or Enantiomer	R3
301	rac	
302	+	
303	-	

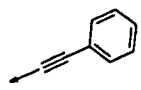
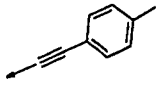
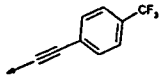
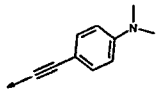
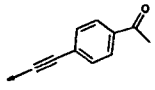
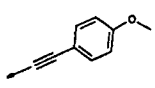
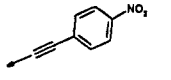
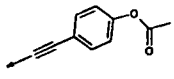
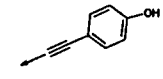
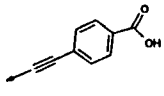


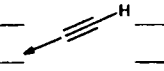
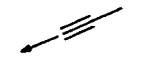
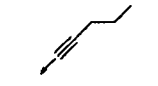
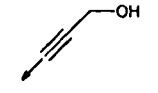
304	rac	
305	+	
306	-	
307	rac	
308	+	
309	-	
310	rac	
311	+	
312	-	
313	rac	
314	+	
315	-	
316	rac	
317	+	
318	-	
319	rac	
320	+	
321	-	
322	rac	
323	+	
324	-	
325	rac	
326	+	
327	-	
328	rac	
329	+	
330	-	
331	rac	
332	+	
333	-	
334	rac	
335	+	
336	-	
337	rac	
338	+	
339	-	
340	rac	
341	+	
342	-	
343	rac	
344	+	
345	-	
346	rac	
347	+	
348	-	
349	rac	
350	+	

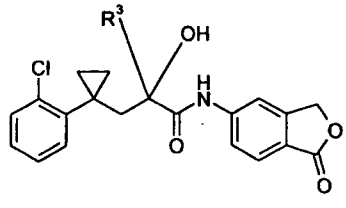
351	-	
352	rac	
353	+	
354	-	
355	rac	
356	+	
357	-	
358	rac	
359	+	
360	-	

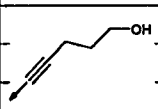
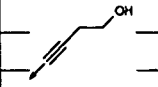
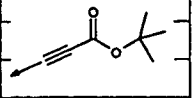
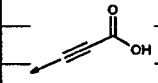
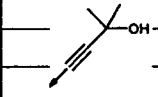
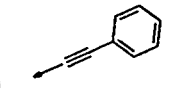
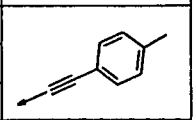
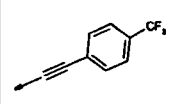
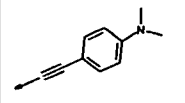
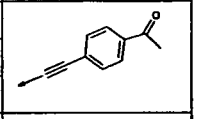
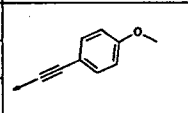
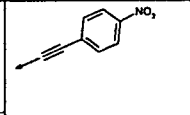
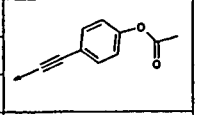
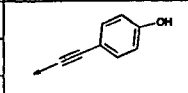
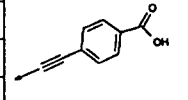


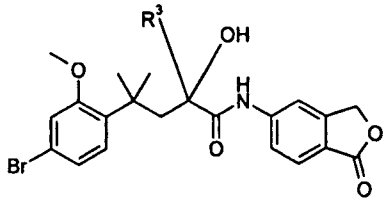
No.	Racemic or Enantiomer	R3
361	rac	
362	+	
363	-	
364	rac	
365	+	
366	-	
367	rac	
368	+	
369	-	
370	rac	
371	+	
372	-	
373	rac	
374	+	
375	-	
376	rac	
377	+	
378	-	
379	rac	
380	+	
381	-	
382	rac	
383	+	
384	-	
385	rac	
386	+	
387	-	
388	rac	
389	+	
390	-	

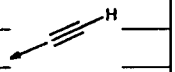
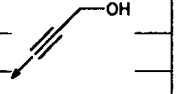
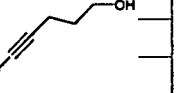
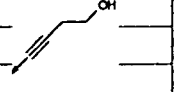
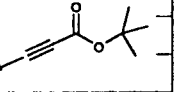
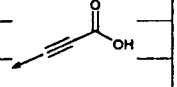
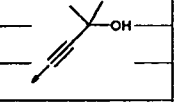
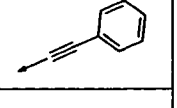
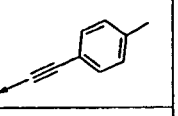
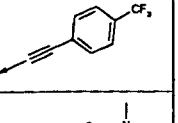
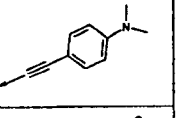
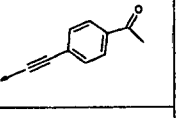
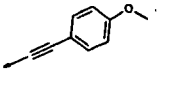
391	rac	
392	+	
393	-	
394	rac	
395	+	
396	-	
397	rac	
398	+	
399	-	
400	rac	
401	+	
402	-	
403	rac	
404	+	
405	-	
406	rac	
407	+	
408	-	
409	rac	
410	+	
411	-	
412	rac	
413	+	
414	-	
415	rac	
416	+	
417	-	
418	rac	
419	+	
420	-	

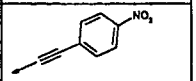
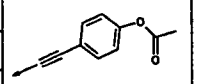
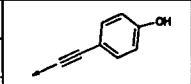
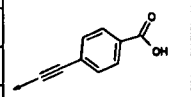
No.	Racemic or Enantiomer	R3
421	rac	
422	+	
423	-	
424	rac	
425	+	
426	-	
427	rac	
428	+	
429	-	
430	rac	
431	+	
432	-	
433	rac	

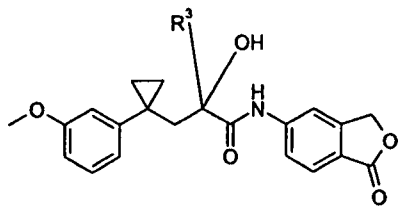


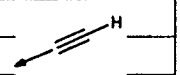
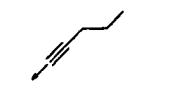
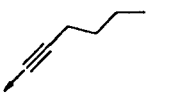
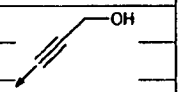
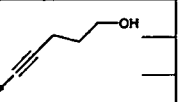
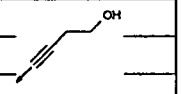
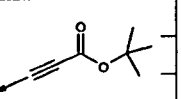
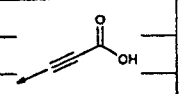
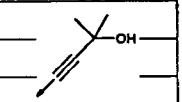
434	+	
435	-	
436	rac	
437	+	
438	-	
439	rac	
440	+	
441	-	
442	rac	
443	+	
444	-	
445	rac	
446	+	
447	-	
448	rac	
449	+	
450	-	
451	rac	
452	+	
453	-	
454	rac	
455	+	
456	-	
457	rac	
458	+	
459	-	
460	rac	
461	+	
462	-	
463	rac	
464	+	
465	-	
466	rac	
467	+	
468	-	
469	rac	
470	+	
471	-	
472	rac	
473	+	
474	-	
475	rac	
476	+	
477	-	
478	rac	
479	+	
480	-	

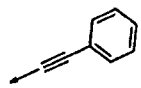
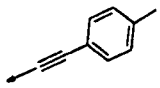
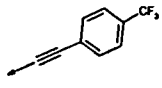
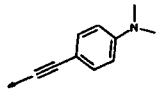
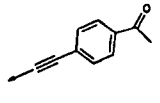
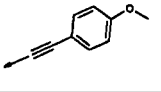
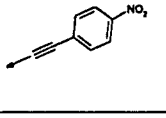
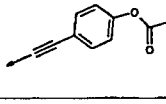
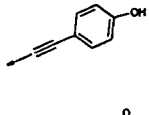
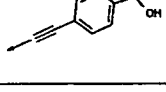


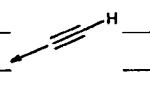
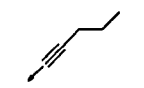
No.	Racemic or Enantiomer	R3
481	rac	
482	+	
483	-	
484	rac	
485	+	
486	-	
487	rac	
488	+	
489	-	
490	rac	
491	+	
492	-	
493	rac	
494	+	
495	-	
496	rac	
497	+	
498	-	
499	rac	
500	+	
501	-	
502	rac	
503	+	
504	-	
505	rac	
506	+	
507	-	
508	rac	
509	+	
510	-	
511	rac	
512	+	
513	-	
214	rac	
515	+	
516	-	
517	rac	
518	+	
519	-	
520	rac	
521	+	
522	-	
523	rac	
524	+	
525	-	
526	rac	

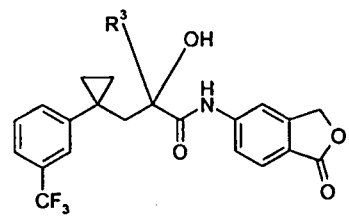
227	+	
528	-	
529	rac	
530	+	
531	-	
532	rac	
533	+	
534	-	
535	rac	
536	+	
537	-	
538	rac	
539	+	
540	-	

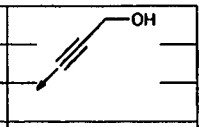
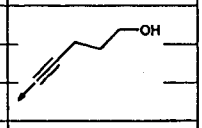
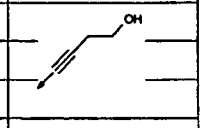
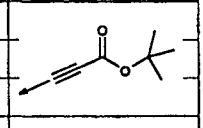
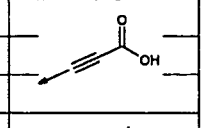
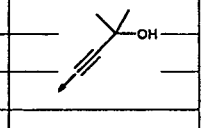
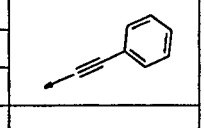
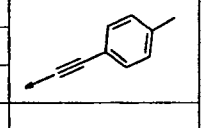
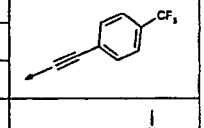
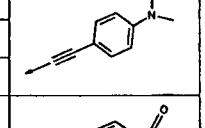
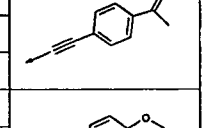
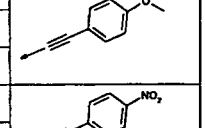
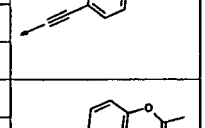
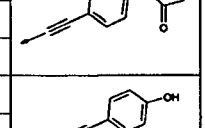
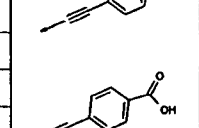
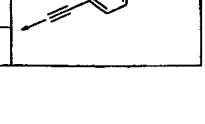


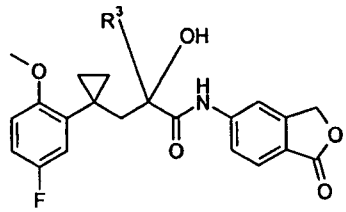
No.	Racemic or Enantiomer	R3
541	rac	
542	+	
543	-	
544	rac	
545	+	
546	-	
547	rac	
548	+	
549	-	
550	rac	
551	+	
552	-	
553	rac	
554	+	
555	-	
556	rac	
557	+	
558	-	
559	rac	
560	+	
561	-	
562	rac	
563	+	
564	-	
565	rac	
566	+	
567	-	
568	rac	
569	+	
570	-	

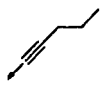
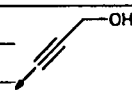
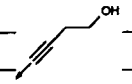
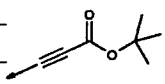
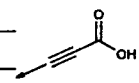
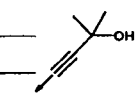
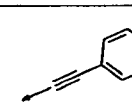
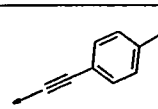
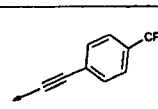
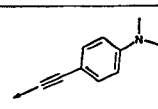
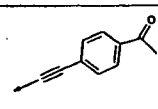
571	rac	
572	+	
573	-	
574	rac	
575	+	
576	-	
577	rac	
578	+	
579	-	
580	rac	
581	+	
582	-	
583	rac	
584	+	
585	-	
586	rac	
587	+	
588	-	
589	rac	
590	+	
591	-	
592	rac	
593	+	
594	-	
595	rac	
596	+	
597	-	
598	rac	
599	+	
600	-	

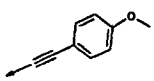
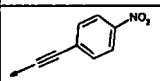
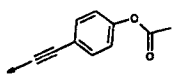
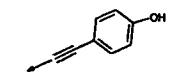
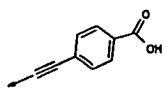
No.	Racemic or Enantiomer	R3
601	rac	
602	+	
603	-	
604	rac	
605	+	
606	-	
607	rac	
608	+	
609	-	
610	rac	
611	+	
612	-	

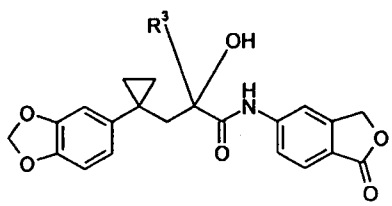


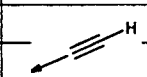
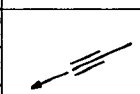
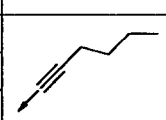
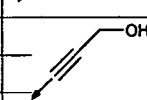
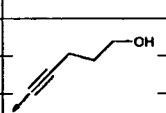
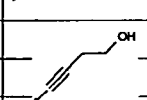
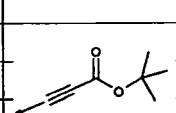
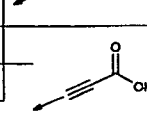
613	rac	
614	+	
615	-	
616	rac	
617	+	
618	-	
619	rac	
620	+	
621	-	
622	rac	
623	+	
624	-	
625	rac	
626	+	
627	-	
628	rac	
629	+	
630	-	
631	rac	
632	+	
633	-	
634	rac	
635	+	
636	-	
637	rac	
638	+	
639	-	
640	rac	
641	+	
642	-	
643	rac	
644	+	
645	-	
646	rac	
647	+	
648	-	
649	rac	
650	+	
651	-	
652	rac	
653	+	
654	-	
655	rac	
656	+	
657	-	
658	rac	
659	+	
660	-	

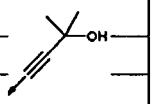
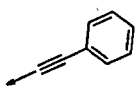
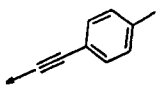
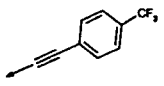
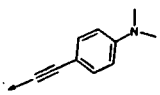
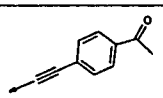
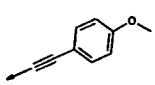
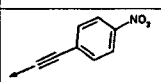
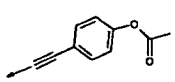
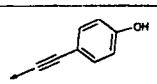
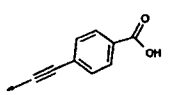


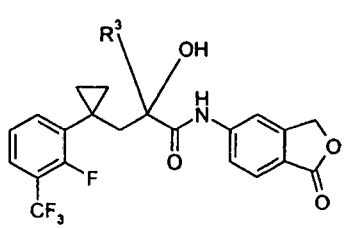
No.	Racemic or Enantiomer	R3
661	rac	
662	+	
663	-	
664	rac	
665	+	
666	-	
667	rac	
668	+	
669	-	
670	rac	
671	+	
672	-	
673	rac	
674	+	
675	-	
676	rac	
677	+	
678	-	
679	rac	
680	+	
681	-	
682	rac	
683	+	
684	-	
685	rac	
686	+	
687	-	
688	rac	
689	+	
690	-	
691	rac	
692	+	
693	-	
694	rac	
695	+	
696	-	
697	rac	
698	+	
699	-	
700	rac	
701	+	
702	-	
703	rac	
704	+	
705	-	

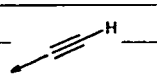
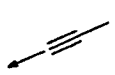
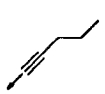
706	rac	
707	+	
708	-	
709	rac	
710	+	
711	-	
712	rac	
713	+	
714	-	
715	rac	
716	+	
717	-	
718	rac	
719	+	
720	-	

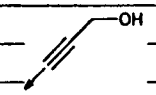
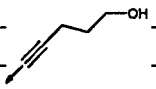
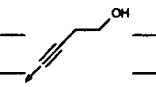
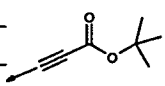
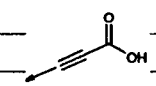
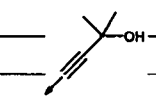
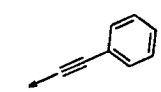
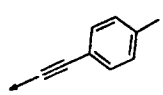
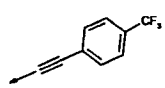
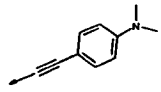
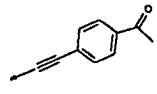
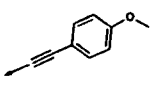
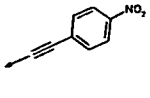
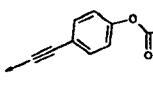
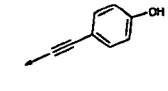


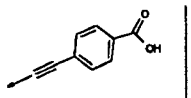
No.	Racemic or Enantiomer	R3
721	rac	
722	+	
723	-	
724	rac	
725	+	
726	-	
727	rac	
728	+	
729	-	
730	rac	
731	+	
732	-	
733	rac	
734	+	
735	-	
736	rac	
737	+	
738	-	
739	rac	
740	+	
741	-	
742	rac	
743	+	
744	-	
745	rac	
746	+	

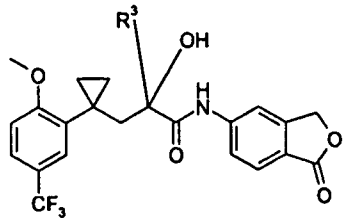
747	-	
748	rac	
749	+	
750	-	
751	rac	
752	+	
753	-	
754	rac	
755	+	
756	-	
757	rac	
758	+	
759	-	
760	rac	
761	+	
762	-	
763	rac	
764	+	
765	-	
766	rac	
767	+	
768	-	
769	rac	
770	+	
771	-	
772	rac	
773	+	
774	-	
775	rac	
776	+	
777	-	
778	rac	
779	+	
780	-	

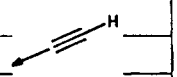
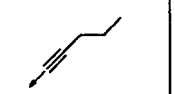
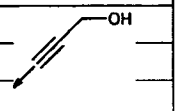
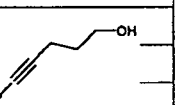
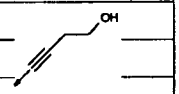
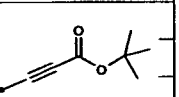
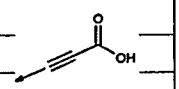
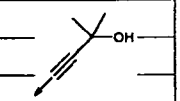
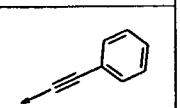
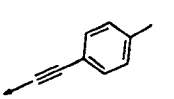
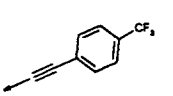


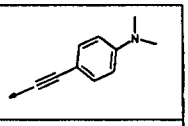
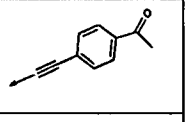
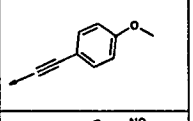
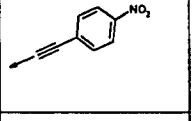
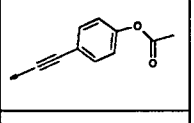
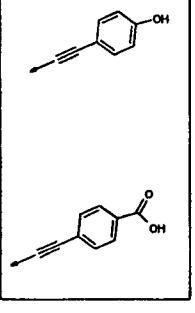
No.	Racemic or Enantiomer	R3
781	rac	
782	+	
783	-	
784	rac	
785	+	
786	-	
787	rac	
788	+	

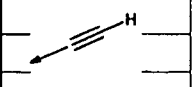
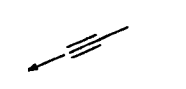
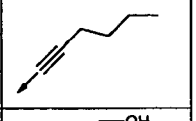
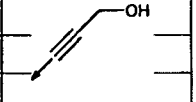
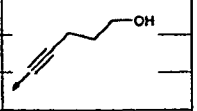
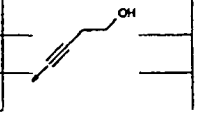
789	-	
790	rac	
791	+	
792	-	
793	rac	
794	+	
795	-	
796	rac	
797	+	
798	-	
799	rac	
800	+	
801	-	
802	rac	
803	+	
804	-	
805	rac	
806	+	
807	-	
808	rac	
809	+	
810	-	
811	rac	
812	+	
813	-	
814	rac	
815	+	
816	-	
817	rac	
818	+	
819	-	
820	rac	
821	+	
822	-	
823	rac	
824	+	
825	-	
826	rac	
827	+	
828	-	
829	rac	
830	+	
831	-	
832	rac	
833	+	
834	-	
835	rac	
836	+	
837	-	

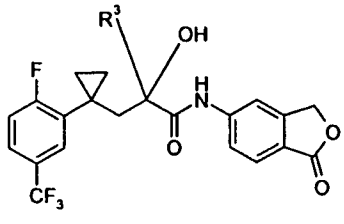
838	rac	
839	+	
840	-	

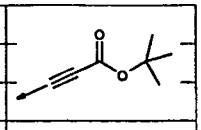
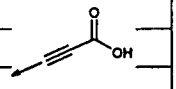
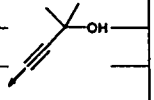
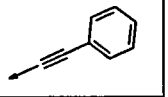
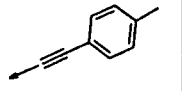
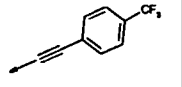
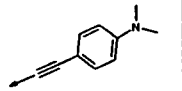
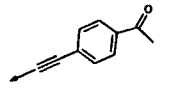
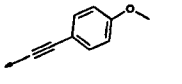
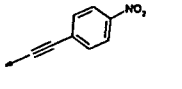
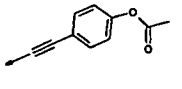
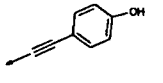
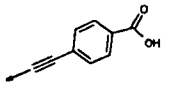


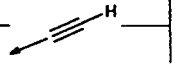
No.	Racemic or Enantiomer	R3
841	rac	
842	+	
843	-	
844	rac	
845	+	
846	-	
847	rac	
848	+	
849	-	
850	rac	
851	+	
852	-	
853	rac	
854	+	
855	-	
856	rac	
857	+	
858	-	
859	rac	
860	+	
861	-	
862	rac	
863	+	
864	-	
865	rac	
866	+	
867	-	
868	rac	
869	+	
870	-	
871	rac	
872	+	
873	-	
874	rac	
875	+	
876	-	
877	rac	
878	+	
879	-	

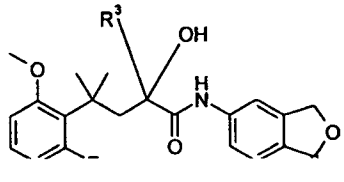
880	rac	
881	+	
882	-	
883	rac	
884	+	
885	-	
886	rac	
887	+	
888	-	
889	rac	
890	+	
891	-	
892	rac	
893	+	
894	-	
895	rac	
896	+	
897	-	
898	rac	
899	+	
900	-	

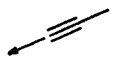
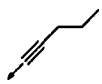
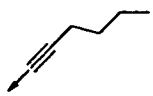
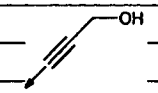
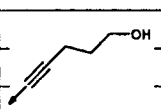
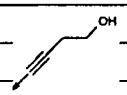
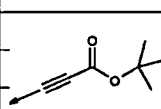
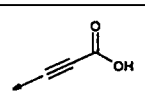
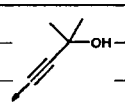
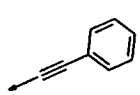
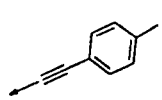
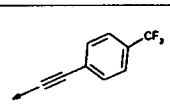
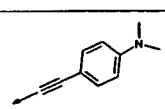
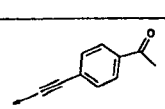
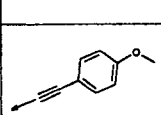
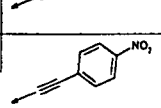
No.	Racemic or Enantiomer	R3
901	rac	
902	+	
903	-	
904	rac	
905	+	
906	-	
907	rac	
908	+	
909	-	
910	rac	
911	+	
912	-	
913	rac	
914	+	
915	-	
916	rac	
917	+	
918	-	
919	rac	
920	+	
921	-	

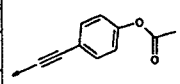
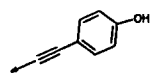
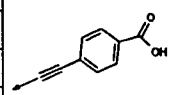


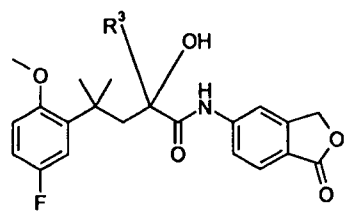
922	rac	
923	+	
924	-	
925	rac	
926	+	
927	-	
928	rac	
929	+	
930	-	
931	rac	
932	+	
933	-	
934	rac	
935	+	
936	-	
937	rac	
938	+	
939	-	
940	rac	
941	+	
942	-	
943	rac	
944	+	
945	-	
946	rac	
947	+	
948	-	
949	rac	
950	+	
951	-	
952	rac	
953	+	
954	-	
955	rac	
956	+	
957	-	
958	rac	
959	+	
960	-	

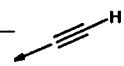
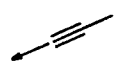
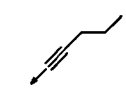
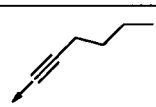
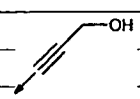
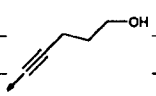
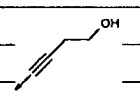
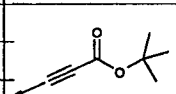
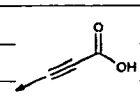
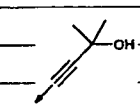
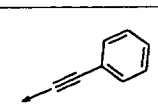
No.	Racemic or Enantiomer	R3
961	rac	
962	+	

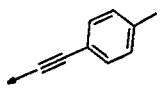
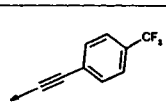
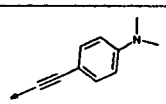
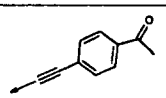
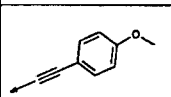
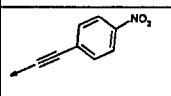
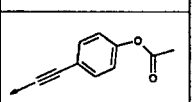
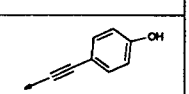
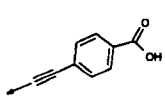


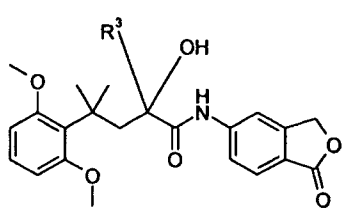
963	-	
964	rac	
965	+	
966	-	
967	rac	
968	+	
969	-	
970	rac	
971	+	
972	-	
973	rac	
974	+	
975	-	
976	rac	
977	+	
978	-	
979	rac	
980	+	
981	-	
982	rac	
983	+	
984	-	
985	rac	
986	+	
987	-	
988	rac	
989	+	
990	-	
991	rac	
992	+	
993	-	
994	rac	
995	+	
996	-	
997	rac	
998	+	
999	-	
1000	rac	
1001	+	
1002	-	
1003	rac	
1004	+	
1005	-	
1006	rac	
1007	+	
1008	-	
1009	rac	

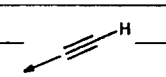
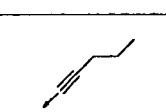
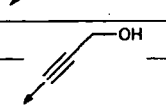
1010	+	
1011	-	
1012	rac	
1013	+	
1014	-	
1015	rac	
1016	+	
1017	-	
1018	rac	
1019	+	
1020	-	

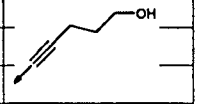
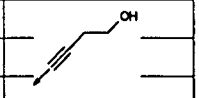
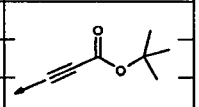
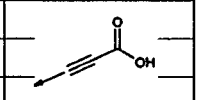
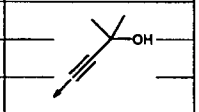
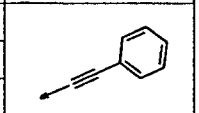
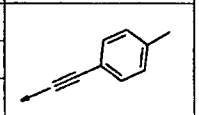
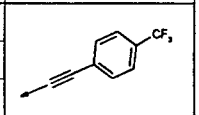
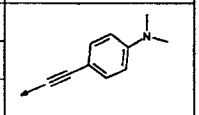
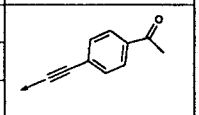
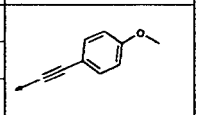
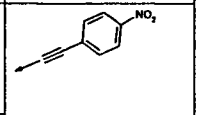
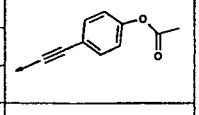
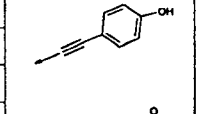
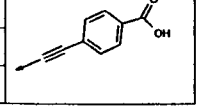


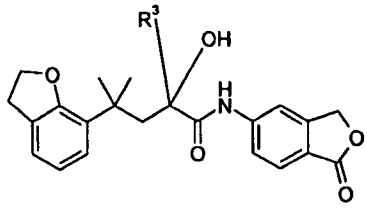
No.	Racemic or Enantiomer	R3
1021	rac	
1022	+	
1023	-	
1024	rac	
1025	+	
1026	-	
1027	rac	
1028	+	
1029	-	
1030	rac	
1031	+	
1032	-	
1033	rac	
1034	+	
1035	-	
1036	rac	
1037	+	
1038	-	
1039	rac	
1040	+	
1041	-	
1042	rac	
1043	+	
1044	-	
1045	rac	
1046	+	
1047	-	
1048	rac	
1049	+	
1050	-	
1051	rac	

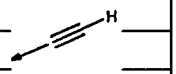
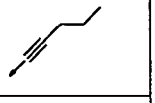
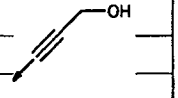
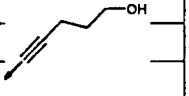
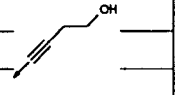
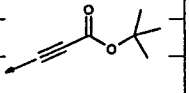
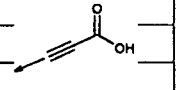
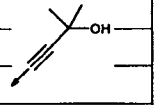
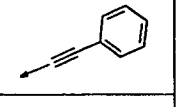
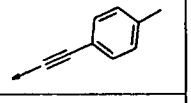
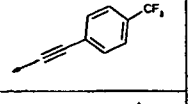
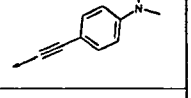
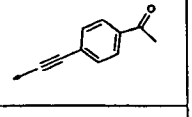
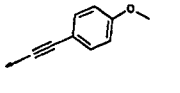
1052	+	
1053	-	
1054	rac	
1055	+	
1056	-	
1057	rac	
1058	+	
1059	-	
1060	rac	
1061	+	
1062	-	
1063	rac	
1064	+	
1065	-	
1066	rac	
1067	+	
1068	-	
1069	rac	
1070	+	
1071	-	
1072	rac	
1073	+	
1074	-	
1075	rac	
1076	+	
1077	-	
1078	rac	
1079	+	
1080	-	

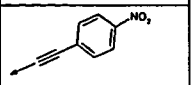
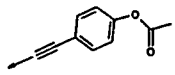
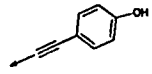
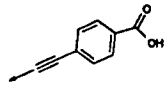


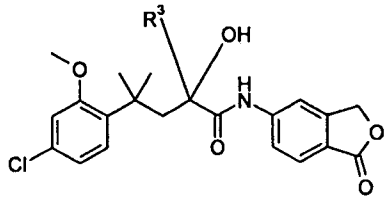
No.	Racemic or Enantiomer	R3
1081	rac	
1082	+	
1083	-	
1084	rac	
1085	+	
1086	-	
1087	rac	
1088	+	
1089	-	
1090	rac	
1091	+	
1092	-	
1093	rac	
1094	+	

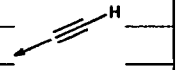
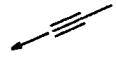
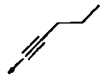
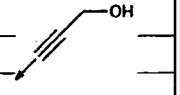
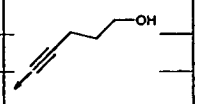
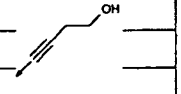
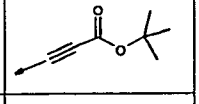
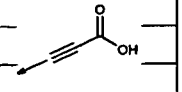
1095	-	
1096	rac	
1097	+	
1098	-	
1099	rac	
1100	+	
1101	-	
1102	rac	
1103	+	
1104	-	
1105	rac	
1106	+	
1107	-	
1108	rac	
1109	+	
1110	-	
1111	rac	
1112	+	
1113	-	
1114	rac	
1115	+	
1116	-	
1117	rac	
1118	+	
1119	-	
1120	rac	
1121	+	
1122	-	
1123	rac	
1124	+	
1125	-	
1126	rac	
1127	+	
1128	-	
1129	rac	
1130	+	
1131	-	
1132	rac	
1133	+	
1134	-	
1135	rac	
1136	+	
1137	-	
1138	rac	
1139	+	
1140	-	

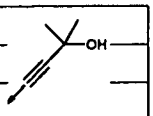
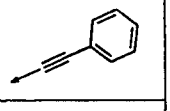
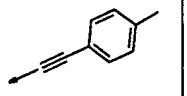
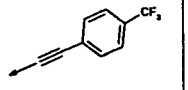
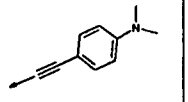
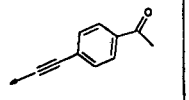
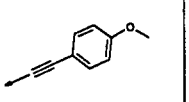
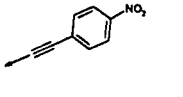
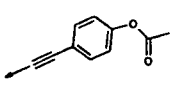
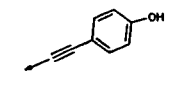
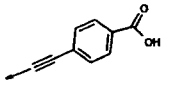


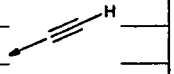
No.	Racemic or Enantiomer	R3
1141	rac	
1142	+	
1143	-	
1144	rac	
1145	+	
1146	-	
1147	rac	
1148	+	
1149	-	
1150	rac	
1151	+	
1152	-	
1153	rac	
1154	+	
1155	-	
1156	rac	
1157	+	
1158	-	
1159	rac	
1160	+	
1161	-	
1162	rac	
1163	+	
1164	-	
1165	rac	
1166	+	
1167	-	
1168	rac	
1169	+	
1170	-	
1171	rac	
1172	+	
1173	-	
1174	rac	
1175	+	
1176	-	
1177	rac	
1178	+	
1179	-	
1180	rac	
1181	+	
1182	-	
1183	rac	
1184	+	
1185	-	
1186	rac	

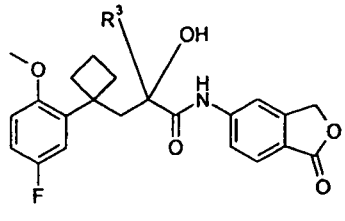
1187	+	
1188	-	
1189	rac	
1190	+	
1191	-	
1192	rac	
1193	+	
1194	-	
1195	rac	
1196	+	
1197	-	
1198	rac	
1199	+	
1200	-	

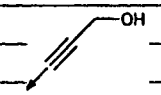
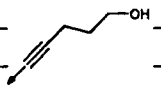
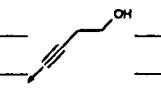
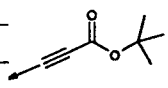
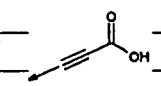
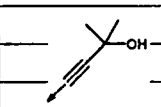
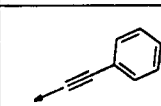
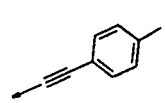
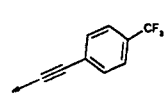
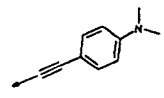
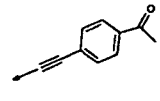
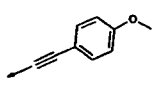
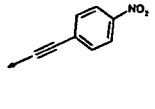
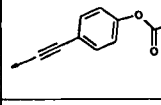
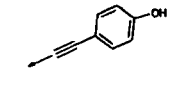


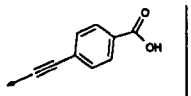
No.	Racemic or Enantiomer	R3
1201	rac	
1202	+	
1203	-	
1204	rac	
1205	+	
1206	-	
1207	rac	
1208	+	
1209	-	
1210	rac	
1211	+	
1212	-	
1213	rac	
1214	+	
1215	-	
1216	rac	
1217	+	
1218	-	
1219	rac	
1220	+	
1221	-	
1222	rac	
1223	+	
1224	-	
1225	rac	
1226	+	
1227	-	

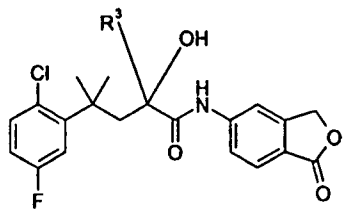
1228	rac	
1229	+	
1230	-	
1231	rac	
1232	+	
1233	-	
1234	rac	
1235	+	
1236	-	
1237	rac	
1238	+	
1239	-	
1240	rac	
1241	+	
1242	-	
1243	rac	
1244	+	
1245	-	
1246	rac	
1247	+	
1248	-	
1249	rac	
1250	+	
1251	-	
1252	rac	
1253	+	
1254	-	
1255	rac	
1256	+	
1257	-	
1258	rac	
1259	+	
1260	-	

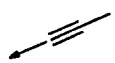
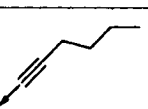
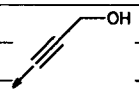
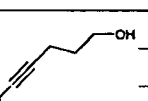
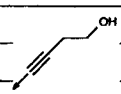
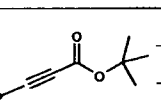
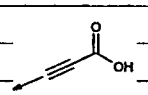
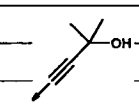
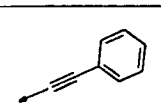
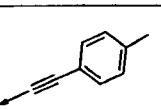
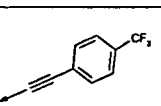
No.	Racemic or Enantiomer	R3
1261	rac	
1262	+	
1263	-	
1264	rac	
1265	+	
1266	-	
1267	rac	
1268	+	

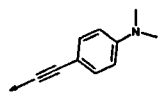
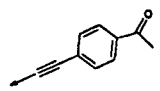
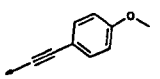
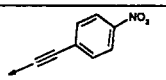
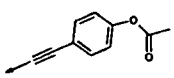
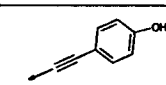
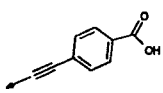


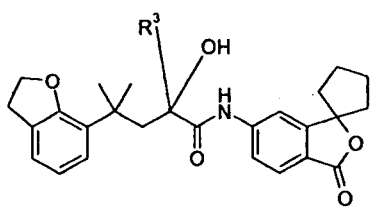
1269	-	
1270	rac	
1271	+	
1272	-	
1273	rac	
1274	+	
1275	-	
1276	rac	
1277	+	
1278	-	
1279	rac	
1280	+	
1281	-	
1282	rac	
1283	+	
1284	-	
1285	rac	
1286	+	
1287	-	
1288	rac	
1289	+	
1290	-	
1291	rac	
1292	+	
1293	-	
1294	rac	
1295	+	
1296	-	
1297	rac	
1298	+	
1299	-	
1300	rac	
1301	+	
1302	-	
1303	rac	
1304	+	
1305	-	
1306	rac	
1307	+	
1308	-	
1309	rac	
1310	+	
1311	-	
1312	rac	
1313	+	
1314	-	
1315	rac	
1316	+	
1317	-	

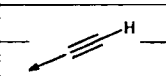
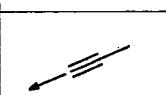
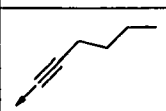
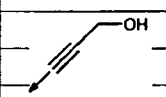
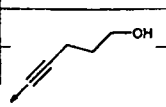
1318	rac	
1319	+	
1320	-	

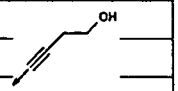
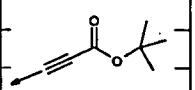
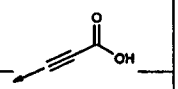
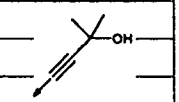
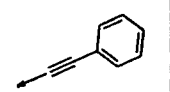
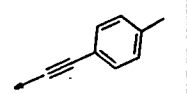
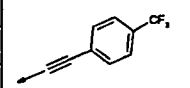
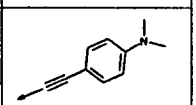
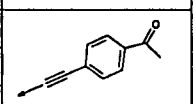
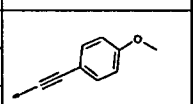
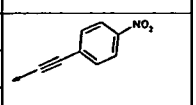
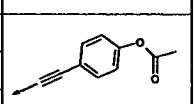
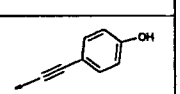
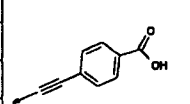


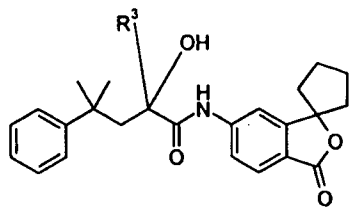
No.	Racemic or Enantiomer	R3
1321	rac	
1322	+	
1323	-	
1324	rac	
1325	+	
1326	-	
1327	rac	
1328	+	
1329	-	
1330	rac	
1331	+	
1332	-	
1333	rac	
1334	+	
1335	-	
1336	rac	
1337	+	
1338	-	
1339	rac	
1340	+	
1341	-	
1342	rac	
1343	+	
1344	-	
1345	rac	
1346	+	
1347	-	
1348	rac	
1349	+	
1350	-	
1351	rac	
1352	+	
1353	-	
1354	rac	
1355	+	
1356	-	
1357	rac	
1358	+	

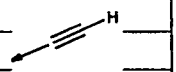
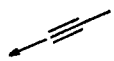
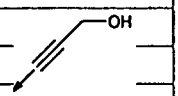
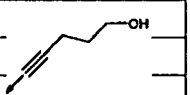
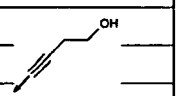
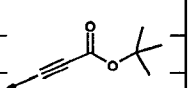
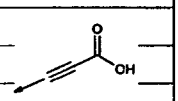
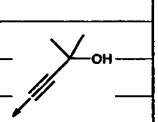
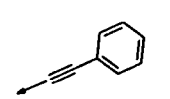
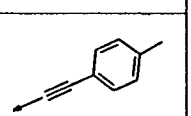
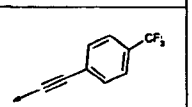
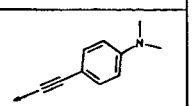
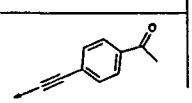
1359	-	
1360	rac	
1361	+	
1362	-	
1363	rac	
1364	+	
1365	-	
1366	rac	
1367	+	
1368	-	
1369	rac	
1370	+	
1371	-	
1372	rac	
1373	+	
1374	-	
1375	rac	
1376	+	
1377	-	
1378	rac	
1379	+	
1380	-	

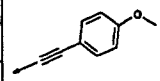
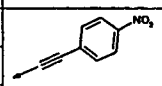
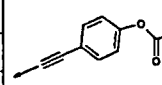
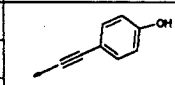
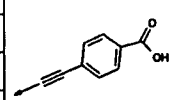


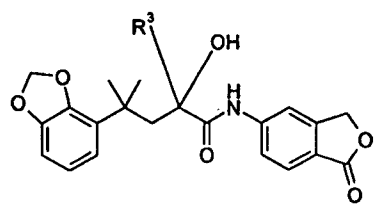
No.	Racemic or Enantiomer	R3
1381	rac	
1382	+	
1383	-	
1384	rac	
1385	+	
1386	-	
1387	rac	
1388	+	
1389	-	
1390	rac	
1391	+	
1392	-	
1393	rac	
1394	+	
1395	-	
1396	rac	
1397	+	

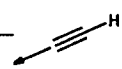
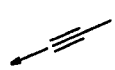
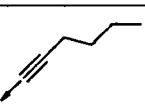
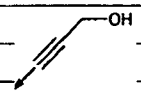
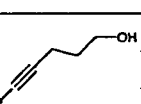
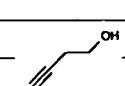
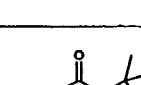
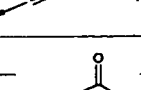
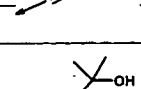
1398	-	
1399	rac	
1400	+	
1401	-	
1402	rac	
1403	+	
1404	-	
1405	rac	
1406	+	
1407	-	
1408	rac	
1409	+	
1410	-	
1411	rac	
1412	+	
1413	-	
1414	rac	
1415	+	
1416	-	
1417	rac	
1418	+	
1419	-	
1420	rac	
1421	+	
1422	-	
1423	rac	
1424	+	
1425	-	
1426	rac	
1427	+	
1428	-	
1429	rac	
1430	+	
1431	-	
1432	rac	
1433	+	
1434	-	
1435	rac	
1436	+	
1437	-	
1438	rac	
1439	+	
1440	-	

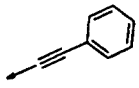
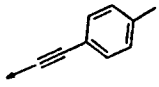
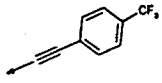
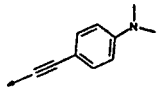
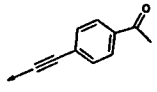
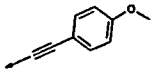
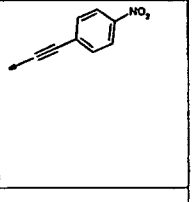
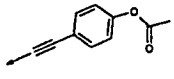
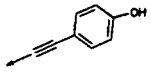
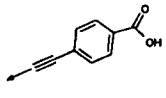


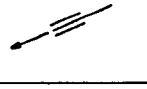
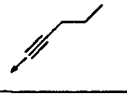
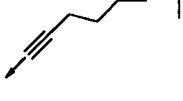
No.	Racemic or Enantiomer	R3
1441	rac	
1442	+	
1443	-	
1444	rac	
1445	+	
1446	-	
1447	rac	
1448	+	
1449	-	
1450	rac	
1451	+	
1452	-	
1453	rac	
1454	+	
1455	-	
1456	rac	
1457	+	
1458	-	
1459	rac	
1460	+	
1461	-	
1462	rac	
1463	+	
1464	-	
1465	rac	
1466	+	
1467	-	
1468	rac	
1469	+	
1470	-	
1471	rac	
1472	+	
1473	-	
1474	rac	
1475	+	
1476	-	
1477	rac	
1478	+	
1479	-	
1480	rac	
1481	+	
1482	-	
1483	rac	
1484	+	

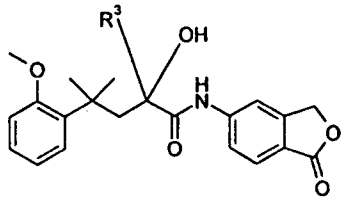
1485	-	
1486	rac	
1487	+	
1488	-	
1489	rac	
1490	+	
1491	-	
1492	rac	
1493	+	
1494	-	
1495	rac	
1496	+	
1497	-	
1498	rac	
1499	+	
1500	-	

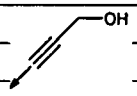
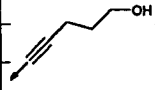
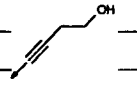
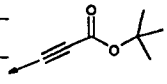
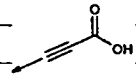
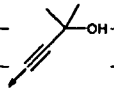
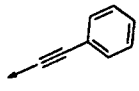
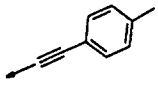
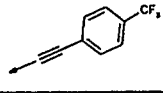
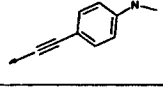
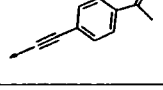
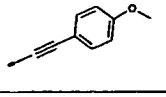
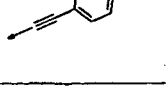
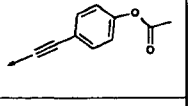
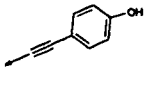


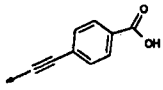
No.	Racemic or Enantiomer	R3
1501	rac	
1502	+	
1503	-	
1504	rac	
1505	+	
1506	-	
1507	rac	
1508	+	
1509	-	
1510	rac	
1511	+	
1512	-	
1513	rac	
1514	+	
1515	-	
1516	rac	
1517	+	
1518	-	
1519	rac	
1520	+	
1521	-	
1522	rac	
1523	+	
1524	-	
1525	rac	
1526	+	
1527	-	
1528	rac	

1529	+	
1530	-	
1531	rac	
1532	+	
1533	-	
1534	rac	
1535	+	
1536	-	
1537	rac	
1538	+	
1539	-	
1540	rac	
1541	+	
1542	-	
1543	rac	
1544	+	
1545	-	
1546	rac	
1547	+	
1548	-	
1549	rac	
1550	+	
1551	-	
1552	rac	
1553	+	
1554	-	
1555	rac	
1556	+	
1557	-	
1558	rac	
1559	+	
1560	-	

No.	Racemic or Enantiomer	R3
1561	rac	
1562	+	
1563	-	
1564	rac	
1565	+	
1566	-	
1567	rac	
1568	+	
1569	-	
1570	rac	



1571	+	
1572	-	
1573	rac	
1574	+	
1575	-	
1576	rac	
1577	+	
1578	-	
1579	rac	
1580	+	
1581	-	
1582	rac	
1583	+	
1584	-	
1585	rac	
1586	+	
1587	-	
1588	rac	
1589	+	
1590	-	
1591	rac	
1592	+	
1593	-	
1594	rac	
1595	+	
1596	-	
1597	rac	
1598	+	
1599	-	
1600	rac	
1601	+	
1602	-	
1603	rac	
1604	+	
1605	-	
1606	rac	
1607	+	
1608	-	
1609	rac	
1610	+	
1611	-	
1612	rac	
1613	+	
1614	-	
1615	rac	
1616	+	
1617	-	

1618	rac	
1619	+	
1620	-	

Biological Characterization of the Compounds According to the Invention

The identification of progesterone receptor modulators can be performed using simple methods, test programs that are known to one skilled in the art. To this end, for example, a compound that is to be tested can be incubated together with a gestagen in a test system for progesterone receptors, and it can be examined whether the progesterone-mediated action in this test system is altered in the presence of modulators.

The substances of general formula I according to the invention were tested in the following models:

Progesterone Receptor Binding Test

Measurement of the Receptor Binding Affinity:

The receptor binding affinity was determined by competitive binding of a specifically binding ^{3}H-labeled hormone (tracer) and the compound to be tested on receptors in the cytosol from animal target organs. In this case, receptor saturation and reaction equilibrium were sought.

The tracers and increasing concentrations of the compound to be tested (competitor) were co-incubated with the receptor-containing cytosol fraction at 0-4°C over 18 hours. After separation of the unbonded tracer with carbon-dextran suspension, the receptor-bonded tracer portion was measured for each concentration, and the IC_{50} was determined from the concentration sequence. As a quotient of the IC_{50} values of the reference substance and the compound to be tested (x 100%), the relative molar binding affinity (RBA) was calculated (RBA of the reference substance = 100%).

For the receptor types, the following incubation conditions were selected:

Progesterone Receptor:

Uterus cytosol of the estradiol-primed rabbit, homogenized in TED buffer (20 mmol of Tris/HCl, pH 7.4; 1 mmol of ethylenediamine tetraacetate, 2 mmol of dithiothreitol) with 250 mmol of saccharose; stored at -30°C. Tracer: ^{3}H-ORG 2058, 5 nmol; reference substance: progesterone.

Glucocorticoid Receptor:

Thymus cytosol of the adrenalectomized rat, thymi stored at -30°C; buffer: TED. Tracer: ^{3}H-Dexamethasone, 20 nmol; reference substance: dexamethasone.

The relative receptor binding affinities (RBA values) of the compounds of general formula (I) according to the invention on the progesterone receptor are between 3 and 100% relative to the progesterone. On the glucocorticoid receptor, the RBA values are in the range of 3 to 30% relative to dexamethasone.

The compounds according to the invention accordingly have a high affinity to the progesterone receptor but only a low affinity to the glucocorticoid receptor.

Antagonism of Progesterone Receptor PR-B

The transactivation assay is performed as described in WO 02/054064.

Agonism of Progesterone Receptor PR-B

The transactivation assay is performed as described in Fuhrmann et al. (Fuhrmann ,U.; Hess-Stump, H.; Cleve, A.; Neef, G.; Schwede, W.; Hoffmann, J.; Fritzemeier, K.-H., Chwalisz, K.; Journal of Medicinal Chem., 43, 26, 2000, 5010-5016).

No.	Antagonistic activity		Agonistic activity	
	IC_{50} [nM]	Efficacy [%]	EC_{50} [nM]	Efficacy [%]
9	3	96	n.b.	3
13	3	92	n.b.	7
3b	0,4	97	n.b.	2
7	4	82	2	11

Dosage

For use according to the invention, the progesterone receptor modulators can be administered orally, enterally, parenterally or transdermally.

In general, satisfactory results can be expected in the treatment of the above-mentioned indications if the daily doses encompass a range of 1 μg to 500 mg of the compound according to the invention.

Suitable dosages of the compounds according to the invention in humans for the treatment of endometriosis, leiomyomas of the uterus and dysfunctional bleeding as well as for use in birth control as well as for hormone replacement therapy are 50 μg to 500 mg per day, depending on age and constitution of the patient, whereby the necessary daily dose can be administered one or more times.

For treatment of breast cancer, the dosage range for the compounds according to the invention comprises 10 mg to 1000 mg daily.

The formulation of the pharmaceutical preparations based on the new compounds is carried out in a way that is known in the art, by the active ingredient being processed with the vehicles, fillers, substances that influence decomposition, binding agents, moisturizers, lubricants, absorbents, diluents, flavoring correctives, dyes, etc., that are commonly used in galenicals and being converted into the desired form of administration.

In this case, reference is made to Remington's Pharmaceutical Science, 15th Ed. Mack Publishing Company, East Pennsylvania (1980).

For oral administration, in particular tablets, film tablets, coated tablets, capsules, pills, powders, granulates, lozenges, suspensions, emulsions or solutions are suitable.

For parenteral administration, injection and infusion preparations are possible.

For intraarticulate injection, correspondingly prepared crystal suspensions can be used.

For intramuscular injection, aqueous and oily injection solutions or suspensions and corresponding depot preparations can be used.

For rectal administration, the new compounds can be used in the form of suppositories, capsules, solutions (e.g., in the form of enemas) and ointments both for systemic therapy and for local therapy.

In addition, agents for vaginal application can also be mentioned as preparations.

For pulmonary administration of the new compounds, the latter can be used in the form of aerosols and inhalants.

For transdermal administration, patches are possible, or for topical application, formulations in gels, ointments, fatty ointments, creams, pastes, powders, milk and tinctures are possible. The dosage of the compounds of general formula I should be 0.01% - 20% in these preparations to achieve an adequate pharmacological action.

Corresponding tablets can be obtained by, for example, mixing active ingredient with known adjuvants, for example inert diluents such as dextrose, sugar, sorbitol, mannitol, polyvinylpyrrolidone, explosives such as corn starch or alginic acid, binders such as starch or gelatin, lubricants such as magnesium stearate or talc and/or agents for achieiving a depot effect such as carboxylpolymethylene, carboxyl methyl cellulose,

cellulose acetate phthalate or polyvinyl acetate. The tablets can also consist of several layers.

Accordingly, coated tablets can be produced by coating cores, produced analogously to the tablets, with agents that are commonly used in tablet coatings, for example polyvinylpyrrolidone or shellac, gum arabic, talc, titanium oxide or sugar. In this case, the coated tablet shell can also consist of several layers, whereby the adjuvants that are mentioned above in the tablets can be used.

Solutions or suspensions of the compounds of general formula I according to the invention can contain additional taste-improving agents such as saccharine, cyclamate or sugar, as well as, e.g., flavoring substances, such as vanilla or orange extract. In addition, they can contain suspending adjuvants such as sodium carboxy methyl cellulose or preservatives such as p-hydroxybenzoates.

The capsules that contain compounds of general formula I can be produced by, for example, the compound(s) of general formula I being mixed with an inert vehicle such as lactose or sorbitol and encapsulated in gelatin capsules.

Suitable suppositories can be produced by, for example, mixing with vehicles that are provided for this purpose, such as neutral fats or polyethylene glycol, or derivatives thereof.

The compounds of general formula (I) according to the invention or their pharmaceutically acceptable salts can be used based on their antagonistic or partial agonistic action for the production of a pharmaceutical agent, in particular for treatment and prophylaxis of gynecological diseases, such as endometriosis, leiomyomas of the uterus, dysfunctional bleeding and dysmenorrhea. In addition, they can be used to counteract hormonal irregularities, to trigger menstruation and alone or in combination with prostaglandins and/or oxytocin to induce birth.

In addition, the compounds of general formula (I) according to the invention or their pharmaceutically acceptable salts are suitable for the production of preparations for contraception for women (see also WO 93/23020, WO 93/21927).

In addition, the compounds according to the invention or their pharmaceutically acceptable salts can be used alone or in combination with a Selective Estrogen Receptor Modulator (SERM) for female hormone replacement therapy.

In addition, the above-mentioned compounds exert an antiproliferative action in hormone-dependent tumors. They are therefore suitable for the therapy of hormone-dependent carcinomas, such as, for example, for breast, prostate or endometrial carcinomas.

The compounds according to the invention or their pharmaceutically acceptable salts can be used for the treatment of hormone-dependent carcinomas, both in first-line therapy and in second-line therapy, in particular after tamoxifen failure.

The compounds of general formula (I) according to the invention that have an antagonistic or partial agonistic action or their pharmaceutically acceptable salts can also be used in combination with compounds that have an antiestrogenic action (estrogen receptor antagonists or aromatase inhibitors) or Selective Estrogen Receptor Modulators (SERM) for the production of pharmaceutical preparations for treating hormone-dependent tumors. For the treatment of endometriosis or leiomyomas of the uterus, the compounds according to the invention can also be used in combination with SERMs or an antiestrogen (estrogen receptor antagonists or aromatase inhibitors). In the treatment of hormone-dependent tumors, the progesterone receptor modulator and the antiestrogen (estrogen receptor antagonists or aromatase inhibitors) or the SERM can be provided for simultaneous or else for sequential administration. In sequential administration, preferably first the antiestrogen (estrogen receptor antagonists or aromatase inhibitor) or SERM is administered, and then the progesterone receptor modulator is administered.

In this case, in the combination with the nonsteroidal progesterone receptor modulators according to the invention, for example, the following antiestrogens (estrogen receptor antagonists or aromatase inhibitors) or SERMs are considered:

tamoxifen, 5-(4-{5-[(RS)-(4,4,5,5,5-pentafluoropentyl)sulfinyl]-pentyloxy}phenyl)-6-phenyl-8,9-dihydro-7H-benzocyclohepten-2-ol (WO 00/03979), ICI 182 780 (7alpha-[9-(4,4,5,5-pentafluoropentylsulfinyl)nonyl]estra-1,3,5(10)-triene-3,17-beta-diol), 11beta-fluoro-7alpha-[5-(methyl{3-[(4,4,5,5,5-pentafluoropentyl)sulfanyl]propyl}amino)pentyl]estra-1,3,5(10)-triene-3,17beta-diol (WO98/07740), 11beta-fluoro-7alpha-{5-[methyl(7,7,8,8,9,9,10,10,10-nonafluorodecyl)amino]pentyl}estra-1,3,5(10)-triene-3,17beta-diol (WO 99/33855), 11beta-fluoro-17alpha-methyl-7alpha-{5-[methyl(8,8,9,9,9-pentafluorononyl)-amino]pentyl}estra-1,3,5(10)-triene-3,17beta-diol (WO 03/045972), clomifene, raloxifene as well as other antiestrogenically active compounds, and aromatase inhibitors, such as, for example, fadrozole, formestane, letrozole, anastrozole or atamestane.

Finally, this invention also relates to the use of the compounds of general formula I, optionally together with an antiestrogen or SERM, for the production of a pharmaceutical agent.

This invention also relates to pharmaceutical compositions that contain at least one compound according to the invention, optionally in the form of a pharmaceutically/pharmacologically compatible salt, without or together with pharmaceutically compatible adjuvants and/or vehicles.

These pharmaceutical compositions and pharmaceutical agents can be provided for oral, rectal, vaginal, subcutaneous, percutaneous, intravenous or intramuscular

administration. In addition to commonly used vehicles and/or diluents, they contain at least one compound according to the invention.

The pharmaceutical agents of the invention are produced in a known way with the commonly used solid or liquid vehicles or diluents and the usually used pharmaceutical-technical adjuvants corresponding to the desired type of administration with a suitable dosage. The preferred preparations exist in a dispensing form that is suitable for oral administration. Such dispensing forms are, for example, tablets, film tablets, coated tablets, capsules, pills, powders, solutions or suspensions or else depot forms.

The pharmaceutical compositions that contain at least one of the compounds according to the invention are preferably administered orally.

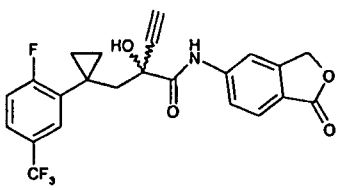
Parenteral preparations, such as injection solutions, are also considered.

In addition, for example, suppositories and agents for vaginal application can also be mentioned as preparations.

The following examples are used for a more detailed explanation of the subject of the invention, without intending that it be limited to these examples.

The production of the starting compound 5-{3-[1-(2-fluoro-5-trifluoromethylphenyl)-cyclopropyl]-2-oxopropionylamino}phthalide is described in Patent WO 200375915, and the production of 5-{3-[1-phenyl-cyclopropyl]-2-oxopropionylamino}phthalide is described in WO 9854159.

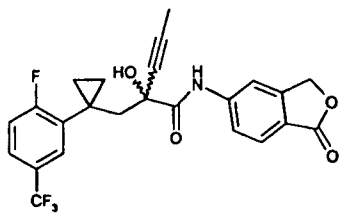
rac-5-{2-Ethinyl-2-hydroxy-3-[1-(2-fluoro-5-trifluoromethylphenyl)-cyclopropyl]-propionylamino}phthalide 1



Ethinyl magnesium bromide (6 ml, 0.5 M in tetrahydrofuran) was added to an ice-cold solution that consists of 5-{3-[1-(2-fluoro-5-trifluoromethylphenyl)-cyclopropyl]-2-oxopropionylamino}phthalide (632 mg) in THF (4 ml). The reaction solution under argon was allowed to come to room temperature within 3 hours. Then, the reaction mixture was poured into ice-cold, saturated ammonium chloride solution. It was extracted with ethyl acetate. The combined organic phases were washed with saturated sodium chloride solution and dried on sodium sulfate. The crude product that is obtained was chromatographed on silica gel. 2.2 g of product was obtained.

^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 0.83 (1H), 0.92-1.10 (2H), 2.37 (1H), 2.56 (1H), 2.59 (1H), 3.10 (1H), 5.28 (2H), 7.02 (1H), 7.31 (1H), 7.37 (1H), 7.58 (1H), 7.86 (1H), 7.94 (1H), 8.70 (1H).

rac-5-{2-Hydroxy-3-[1-(2-fluoro-5-trifluoromethylphenyl)-cyclopropyl]-2-propinyl-propionylamino}phthalide 2

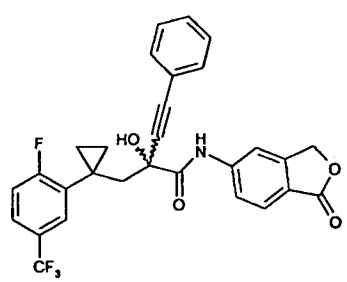


Analogously to Example 1, 145 mg of product was obtained from 1-propinylmagnesium bromide (2 ml of 0.5 M solution in tetrahydrofuran) and 210 mg of 6-[4-(2-chloro-4-fluorophenyl)-4-methyl-2-oxovaleroylamino]-4-methyl-2,3-benzoxazin-1-one.

^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 0.86 (1H), 0.90-1.05 (3H), 1.72 (3H), 2.35 (1H), 2.49 (1H), 2.96 (1H), 5.27 (2H), 7.03 (1H), 7.30 (1H), 7.36 (1H), 7.58 (1H), 7.85 (1H), 7.98 (1H), 8.73 (1H).

(+)-5-{2-Hydroxy-3-[1-(2-fluoro-5-trifluoromethylphenyl)-cyclopropyl]-2-phenyl-propionylamino}phthalide 3a and

(-)-5-{2-Hydroxy-3-[1-(2-fluoro-5-trifluoromethylphenyl)-cyclopropyl]-2-(phenylethinyl)-propionylamino}phthalide 3b



n-Butyllithium (625 µl, 1.6 M in hexane) was added at -78°C to a solution of 110 µl of phenylacetylene in tetrahydrofuran. Stirring was allowed to continue at this temperature for 30 minutes, and then a solution of 5-{3-[1-(2-fluoro-5-

trifluoromethylphenyl)-cyclopropyl]-2-oxopropionylamino}phthalide (210 mg) in 5 ml of tetrahydrofuran was added in drops. Then, it was allowed to come to 23°C over about 3 hours and then stirred for 10 more hours. Then, the reaction mixture was poured into ice-cold, saturated ammonium chloride solution. It was extracted with ethyl acetate. The combined organic phases were washed with saturated sodium chloride solution and dried on sodium sulfate. The crude product was chromatographed on silica gel. The racemic mixture obtained was then separated by preparative chiral HPLC (Chiralpak AD column, 250x10 mm) into enantiomers 3a (46 mg) and 3b (47 mg).

3a and **3b**:

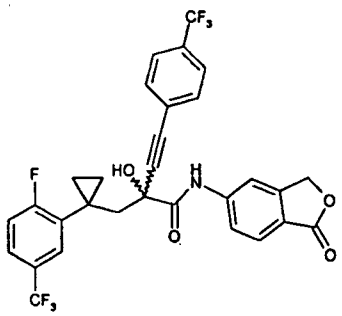
^{1}H-NMR (ppm, $CDCl_3$, 300 MHz): 0.88 (1H), 0.95-1.11 (3H), 2.46 (1H), 2.65 (1H), 3.10 (1H), 5.27 (2H), 7.00 (1H), 7.24-7.42 (7H), 7.61 (1H), 7.84 (1H), 7.98 (1H), 8.80 (1H).

3a : $[\alpha]^D_{20}$: + 12.9° ($CHCl_3$, 1.06 g/100 ml; λ=589 nM)

3b : $[\alpha]^D_{20}$: - 14.4° ($CHCl_3$, 1.03 g100 ml; λ=589 nM)

Analogously to Example 3, compounds 4 and 5 were produced from 5-{3-[1-(2-fluoro-5-trifluoromethylphenyl)-cyclopropyl]-2-oxopropionylamino}phthalide and the respective lithium aryl acetylide.

rac-5-{2-Hydroxy-3-[1-(2-fluoro-5-trifluoromethylphenyl)-cyclopropyl]-2-[(4-trifluoromethylphenyl)ethinyl]propionylamino}phthalide 4



^{1}H-NMR (ppm, $CDCl_3$, 300 MHz): 0.92 (1H), 0.99-1.16 (3H), 2.55 (1H), 2.68 (1H), 3.27 (1H), 5.30 (2H), 7.03 (1H), 7.30-7.52 (4H), 7.55-7.62 (2H), 6.67 (1H), 7.99 (1H), 8.03 (1H), 8.84 (1H).

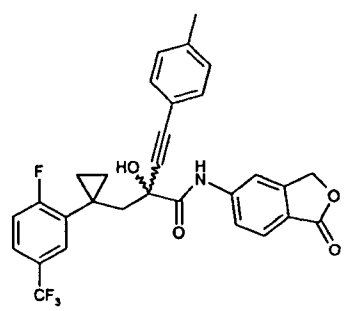
(+)-5-{2-Hydroxy-3-[1-(2-fluoro-5-trifluormethylphenyl)-cyclopropyl]-2-[(4-trifluormethylphenyl)ethinyl]propionylamino}phthalide 4a and (-)-5-{2-Hydroxy-3-[1-(2-fluoro-5-trifluormethylphenyl)-cyclopropyl]-2-[(4-trifluormethylphenyl)ethinyl]propionylamino}phthalide 4b

The racemic mixture (150 mg) which was described in example **4** was separated by preparative chiral HPLC (column Chiralpak AD 250x10 mm) into the enantiomers **4a** (51 mg) and **4b** (62 mg).

4a : $[\alpha]^D_{20}$: + 6.3° ($CHCl_3$, 1.07 g/100 ml; λ=589 nM)

4b : $[\alpha]^D_{20}$: - 5.3° ($CHCl_3$, 1.09 g100 ml; λ=589 nM)

rac-5-{2-Hydroxy-3-[1-(2-fluoro-5-trifluoromethylphenyl)-cyclopropyl]-2-[(4-methylphenyl)ethinyl]propionylamino}phthalide 5



^{1}H-NMR (ppm, $CDCl_3$, 300 MHz): 0.87 (1H), 0.93-1.15 (3H), 2.38 (3H), 2.45 (1H), 2.66 (1H), 3.11 (1H), 5.25 (2H), 6.99 (1H), 7.10 (2H), 7.18-7.38 (4H), 7.61 (1H), 7.86 (1H), 8.00 (1H), 8.80 (1H).

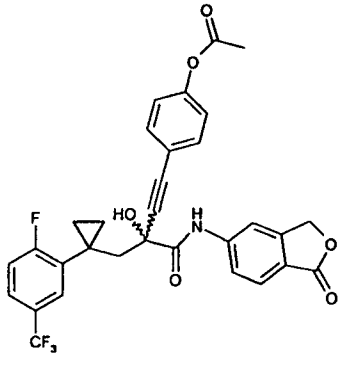
(+)-5-{2-Hydroxy-3-[1-(2-fluoro-5-trifluoromethylphenyl)-cyclopropyl]-2-[(4-methylphenyl)ethinyl]propionylamino}phthalide 5a and (-)-5-{2-Hydroxy-3-[1-(2-fluoro-5-trifluoromethylphenyl)-cyclopropyl]-2-[(4-methylphenyl)ethinyl]propionylamino}phthalide 5b

The racemic mixture (109 mg) which was described in example **5** was separated by preparative chiral HPLC (column Chiralpak AD 250x10 mm) into the enantiomers **5a** (41 mg) and **5b** (28 mg).

5a : $[\alpha]^{D}_{20}$: + 14.8° ($CHCl_3$, 1.07 g/100 ml; λ=589 nM)

5b : $[\alpha]^{D}_{20}$: - 16.3° ($CHCl_3$, 1.13 g100 ml; λ=589 nM)

rac-5-{2-[(4-Acetoxyphenyl)ethinyl]-2-hydroxy-3-[1-(2-fluoro-5-trifluoromethylphenyl)-cyclopropyl]-propionylamino}phthalide 6

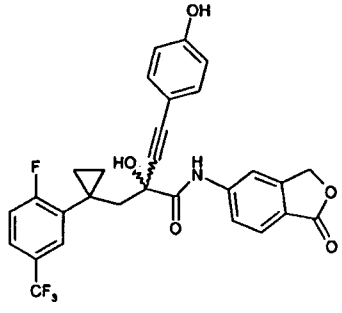


A suspension of the compound (104 mg) described under Example 1, triphenylphosphine (12.2 mg), copper iodide (8.9 mg), 4-iodophenyl acetate (92 mg), palladium acetate (5.3 mg) in THF (5 ml) and triethylamine (5 ml) was reacted for 1 hour in an ultrasound bath at 25°C under argon. Then, it was poured into saturated, aqueous ammonium chloride solution. It was extracted with ethyl acetate and washed with water and saturated sodium chloride solution. The combined organic phases were

dried on sodium sulfate. After column chromatography of the crude product on silica gel, 55 mg of product was obtained.

^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 0.88 (1H), 0.95-1.10 (3H), 2.29 (3H), 2.45 (1H), 2.63 (1H), 3.17 (1H), 5.29 (2H), 6.97-7.07 (3H), 7.28-7.37 (4H), 7.60 (1H), 7.84 (1H), 7.98 (1H), 8.80 (1H).

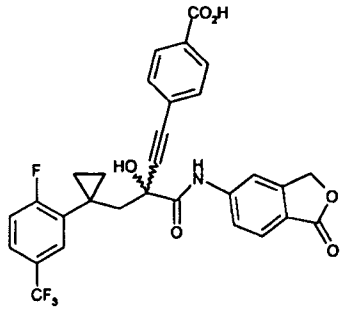
rac-5-{2-Hydroxy-2-[(4-hydroxyphenyl)ethinyl]-3-[1-(2-fluoro-5-trifluoromethylphenyl)- cyclopropyl]-propionylamino}phthalide 7



A solution of the compound described under 6 (45 mg) in 5 ml of methanol was mixed with sodium bicarbonate (130 mg). Stirring was continued for 2 more hours at 23°C. Then, the reaction mixture was diluted with ethyl acetate. Then, it was washed twice with saturated sodium chloride solution. After drying on sodium sulfate, the crude product was purified on silica gel by column chromatography. 38 mg of product was obtained.

^{1}H-NMR (ppm, $CDCl_3$, 300 MHz): 0.87 (1H), 0.92-1.11 (3H), 2.43 (1H), 2.64 (1H), 3.11 (1H), 5.27 (2H), 5.67 (1H), 6.73 (2H), 6.98 (1H), 7.14 (2H), 7.28-7.38 (2H), 7.60 (1H), 7.85 (1H), 7.97 (1H), 8.84 (1H).

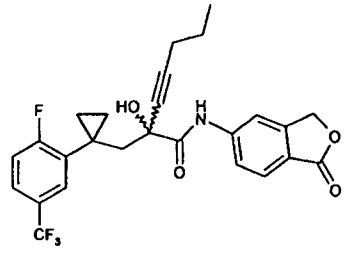
rac-5-{2-[(4-Carboxyphenyl)ethinyl]-2-hydroxy-3-[1-(2-fluoro-5-trifluoromethylphenyl)- cyclopropyl]-propionylamino}phthalide 8



Analogously to Example 6, compound 8 was produced from the compound described under Example 1 and 4-iodobenzoic acid.

^{1}H-NMR (ppm, $CDCl_3$/MeOD (5%), 400 MHz): 0.82 (1H), 0.89-1.05 (3H), 2.37 (1H), 2.65 (1H), 5.24 (2H), 6.97 (1H), 7.35 (1H), 7.44 (2H), 7.50-7.65 (2H), 7.72 (1H), 7.80 (1H), 7.92 (2H).

rac-5-{2-Hydroxy-3-[1-(2-fluoro-5-trifluoromethylphenyl)-cyclopropyl]-2-(pentin-1-yl)-propionylamino}phthalide 9



A solution that consists of 1-pentyne (0.94 ml) in THF (9 ml) was mixed at–78°C with nBuLi (0.6 ml, 1.6 M in hexane). It was allowed to stir for 30 minutes at –78°C, and then a solution of 5-{3-[1-(2-fluoro-5-trifluoromethylphenyl)-cyclopropyl]-2-oxopropionylamino}phthalide (200 mg) in 3 ml of tetrahydrofuran was added. Then, it was allowed to come to 23°C over about 3 hours, and it was stirred for 10 more hours at this temperature. Then, the reaction mixture was poured into ice-cold, saturated ammonium chloride solution. It was extracted with ethyl acetate. The combined organic phases were washed with saturated sodium chloride solution and dried on

sodium sulfate. The crude product was chromatographed on silica gel. 130 mg of product was obtained.

^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 0.82 (1H), 0.92-1.07 (6H), 1.45 (2H), 2.08 (2H), 2.30 (1H), 2.53 (1H), 2.83 (1H), 5.27 (2H), 7.02 (1H), 7.29 (1H), 7.36 (1H), 7.57 (1H), 7.84 (1H), 7.96 (1H), 8.72 (1H).

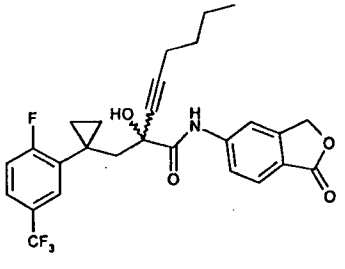
(+)-5-{2-Hydroxy-3-[1-(2-fluoro-5-trifluoromethylphenyl)-cyclopropyl]-2-(pentin-1-yl)-propionylamino}phthalide 9a and
(-)-5-{2-Hydroxy-3-[1-(2-fluoro-5-trifluoromethylphenyl)-cyclopropyl]-2-(pentin-1-yl)-propionylamino}phthalide 9b

The racemic mixture (120 mg) which was described in example **9** was separated by preparative chiral HPLC (column Chiralpak AD 250x10 mm) into the enantiomers **9a** (46 mg) and **9b** (47 mg).

9a : $[\alpha]^D_{20}$: + 10.9° ($CHCl_3$, 1.01 g/100 ml; λ=589 nM)

9b : $[\alpha]^D_{20}$: - 10.6° ($CHCl_3$, 1.08 g100 ml; λ=589 nM)

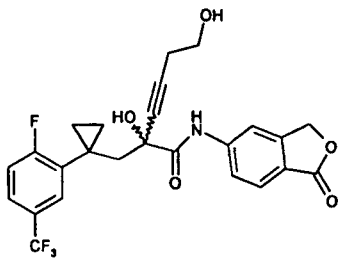
rac-5-{2-Hydroxy-3-[1-(2-fluoro-5-trifluoromethylphenyl)-cyclopropyl]-2-(hexin-1-yl)-propionylamino}phthalide 10



Compound 10 was synthesized analogously to Example 9.

^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 0.80-1.06 (7H), 1.30-1.50 (2H), 1.59 (2H), 2.10 (2H), 2.30 (1H), 2.52 (1H), 2.82 (1H), 5.28 (2H), 7.02 (1H), 7.30 (1H), 7.36 (1H), 7.57 (1H), 7.84 (1H), 7.95 (1H), 8.72 (1H).

rac-5-{2-Hydroxy-3-[1-(2-fluoro-5-trifluoromethylphenyl)-cyclopropyl]-2-[(4-hydroxy)butin-1-yl]-propionylamino}phthalide 11



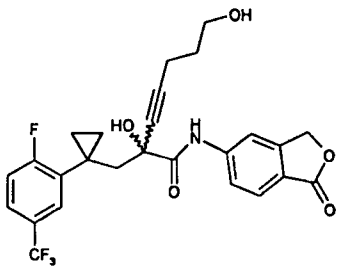
Stage A: Reaction of 4-(tert-butyldimethylsilyloxo)but-1-yne (175 mg), nBuLi (0.59 ml, 1.6 M in hexane) 5-{3-[1-(2-Fluoro-5-trifluoromethylphenyl)-cyclopropyl]-2-oxopropionylamino}-phthalide (200 mg) in tetrahydrofuran analogously to the process described under Example 9 yielded 165 mg of product.

Stage B: The product obtained under stage A (160 mg) was dissolved in 5 ml of tetrahydrofuran. At 0°C, 270 µl of a 1 molar solution of tetrabutylammonium fluoride in tetrahydrofuran was added and stirred for one hour at 0°C and for another 2 hours at 23°C. Then, the reaction mixture was poured into saturated, aqueous sodium bicarbonate solution. It was extracted several times with ethyl acetate. The combined organic phases were washed with saturated sodium chloride solution and dried on sodium sulfate. After column chromatography on silica gel, 77 mg of product was obtained.

^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 0.83 (1H), 0.90-1.03 (3H), 2.20-2.40 (3H), 2.50 (1H), 3.39 (1H), 3.68 (2H), 5.25 (2H), 7.01 (1H), 7.32 (2H), 7.57 (1H), 7.82 (1H), 7.93 (1H), 8.91 (1H).

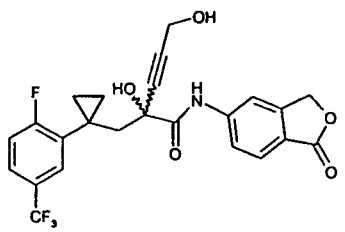
Analogously to Example 11, compounds 12 and 13 were produced from 5-{3-[1-(2-fluoro-5-trifluoromethylphenyl)-cyclopropyl]-2-oxopropionylamino}phthalide:

rac-5-{2-Hydroxy-3-[1-(2-fluoro-5-trifluoromethylphenyl)-cyclopropyl]-2-[(5-hydroxy)pentin-1-yl]-propionylamino}phthalide 12



^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 0.83 (1H), 0.90-1.03 (3H), 1.70 (2H), 2.24 (2H), 2.33 (1H), 2.50 (1H), 3.09 (1H), 3.71 (2H), 5.26 (2H), 7.02 (1H), 7.35 (2H), 7.57 (1H), 7.83 (1H), 7.97 (1H), 8.82 (1H).

rac-5-{2-Hydroxy-3-[1-(2-fluoro-5-trifluoromethylphenyl)-cyclopropyl]-2-[(3-hydroxy)propin-1-yl]-propionylamino}phthalide 13



^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 0.84 (1H), 0.90-1.03 (3H), 2.37 (1H), 2.52 (1H), 3.25 (1H), 4.17 (2H), 5.27 (2H), 7.02 (1H), 7.30-7.40 (2H), 7.58 (1H), 7.83 (1H), 7.91 (1H), 8.77 (1H).

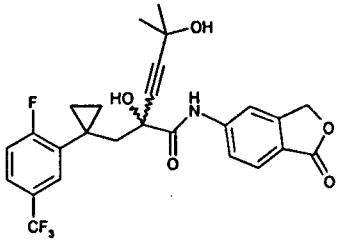
(+)-5-{2-Hydroxy-3-[1-(2-fluoro-5-trifluoromethylphenyl)-cyclopropyl]-2-[(3-hydroxy)propin-1-yl]-propionylamino}phthalide 13a and
(-)-5-{2-Hydroxy-3-[1-(2-fluoro-5-trifluoromethylphenyl)-cyclopropyl]-2-[(3-hydroxy)propin-1-yl]-propionylamino}phthalide 13b

The racemic mixture (80 mg) which was described in example **13** was separated by preparative chiral HPLC (column Chiralpak AD 250x10 mm) into the enantiomers **13a** (35 mg) and **13b** (37 mg).

13a : $[\alpha]^{D}_{20}$: + 28.3° ($CHCl_3$, 1.01 g/100 ml; λ=589 nM)

13b : $[\alpha]^{D}_{20}$: - 29.3° ($CHCl_3$, 1.08 g100 ml; λ=589 nM)

rac-5-{2-Hydroxy-3-[1-(2-fluoro-5-trifluoromethylphenyl)-cyclopropyl]-2-[(4-hydroxy-3-methyl)butin-1-yl]-propionylamino}phthalide 14

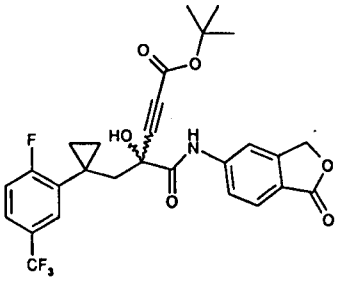


Stage A: Analogously to Example 11, 300 mg of 5-{3-[1-(2-fluoro-5-trifluoromethylphenyl)-cyclopropyl]-2-oxopropionylamino}phthalide and 282 mg of tert-butyl-(1,1-dimethylprop-2-ynyl-oxy)-dimethylsilane are reacted. 15 mg of product A is obtained.

Stage B: 70 mg of the compound that is obtained under A was dissolved in 1 ml of dichloromethane. 650 µl of trifluoroacetic acid (20% in dichloromethane) was added at 0°C, and it was stirred for 3.5 hours at 0°C. Then, it was evaporated to the dry state in a vacuum, and the residue was purified by column chromatography on silica gel. 27 mg of product was obtained.

^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 0.82 (1H), 0.90-1.00 (2H), 1.04 (1H), 1.47 (6H), 2.28 (1H), 2.58 (1H), 3.08 (1H), 5.27 (2H), 7.03 (1H), 7.30 (1H), 7.36 (1H), 7.59 (1H), 7.83 (1H), 7.91 (1H), 8.78 (1H).

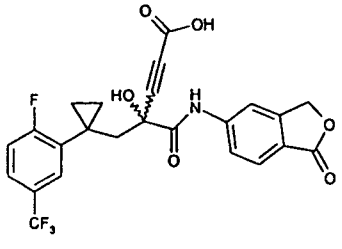
rac-5-{2-Hydroxy-3-[1-(2-fluoro-5-trifluoromethylphenyl)-cyclopropyl]-2-(2-(tert-butylcarboxy)ethin-1-yl)-propionylamino}phthalide 15



Compound 15 was synthesized analogously to Example 9.

^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 0.87 (1H), 0.93-1.05 (3H), 1.46 (9H), 2.42 (1H), 2.59 (1H), 3.39 (1H), 5.28 (2H), 7.03 (1H), 7.30-7.42 (2H), 7.57 (1H), 7.85 (1H), 7.92 (1H), 8.68 (1H).

rac-5-{2-Hydroxy-3-[1-(2-fluoro-5-trifluoromethylphenyl)-cyclopropyl]-2-(2-carboxyethin-1-yl)-propionylamino}phthalide 16

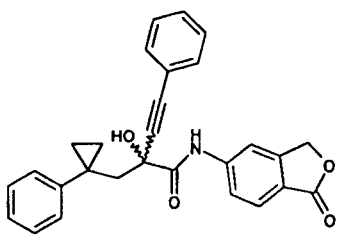


50 mg of the compound that is described under Example 15 was dissolved in 5 ml of dichloromethane. 100 µl of trifluoroacetic acid was added, and it was stirred for 12 more hours at 23°C. Then, it was evaporated to the dry state in a vacuum, and the residue was purified by column chromatography on silica gel. 36 mg of product was obtained.

^{1}H-NMR (ppm, DMSO-D_6, 300 MHz): 0.48 (1H), 0.78 (1H), 0.86 (1H), 1.09 (1H), 1.73 (1H), 2.89 (1H), 5.27 (2H), 6.62 (1H), 7.13 (1H), 7.31 (1H), 7.41 (1H), 7.53 (1H), 7.62 (1H), 7.68 (1H), 9.85 (1H).

Analogously to Example 3, compound 17 was produced from 5-{3-[1-phenyl-cyclopropyl]-2-oxopropionylamino}phthalide:

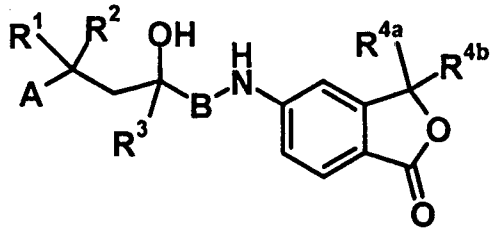
rac-5-{2-Hydroxy-3-[1-phenyl-cyclopropyl]-2-(phenyl-ethinyl)propionylamino}-phthalide 17



^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 0.78 (1H), 0.90 (1H), 1.10-1.21 (2H), 2.38 (1H), 2.72 (1H), 2.77 (1H), 5.28 (2H), 7.18 (1H), 7.25-7.42 (6H), 7.41-7.52 (4H), 7.82 (1H), 8.06 (1H), 8.79 (1H).

Claims

1. Compounds of general formula I



(I),

in which

R^1 and R^2, independently of one another, mean a hydrogen atom, a straight or nonstraight, branched or unbranched C_1-C_5-alkyl group, also together with the C atom of the chain forming a ring with a total of 3-7 members,

R^3 means a radical C≡C-R^a, whereby

R^a means a hydrogen or a C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkinyl, C_3-C_{10}-cycloalkyl, or heterocycloalkyl that optionally is substituted in one or more places, in the same way or differently, with K, or an aryl or heteroaryl that optionally is substituted in one or more places, in the same way or differently, with L,

K is a cyano, halogen, hydroxy, nitro, -C(O)R^b, CO_2R^b, –O-R^b, -S-R^b, $SO_2NR^cR^d$, -C(O)-NR^cR^d, -OC(O)-NR^cR^d, or -C=NOR^b -NR^cR^d or a C_3-C_{10}-cycloalkyl that optionally is substituted in one or more places, in the same way or differently, with M, heterocycloalkyl, or aryl or heteroaryl that optionally is substituted in one or more places with L,

L means C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkinyl, C_1-C_6-

perfluoroalkyl, C_1-C_6-perfluoroalkoxy, C_1-C_6-alkoxy-C_1-C_6-alkoxy, $(CH_2)_p$-C_3-C_{10}-cycloalkyl, $(CH_2)_p$-heterocycloalkyl, $(CH_2)_pCN$, $(CH_2)_pHal$, $(CH_2)_pNO_2$, $(CH_2)_p$-C_6-C_{12}-aryl, $(CH_2)_p$-heteroaryl, $-(CH_2)_pPO_3(R^b)_2$, $-(CH_2)_pNR^cR^d$, $-(CH_2)_pNR^eCOR^b$, $-(CH_2)_pNR^eCSR^b$, $-(CH_2)_pNR^eS(O)R^b$, $-(CH_2)_pNR^eS(O)_2R^b$, $-(CH_2)_pNR^eCONR^cR^d$, $-(CH_2)_pNR^eCOOR^b$, $-(CH_2)_pNR^eC(NH)NR^cR^d$, $-(CH_2)_pNR^eCSNR^cR^d$, $-(CH_2)_pNR^eS(O)NR^cR^d$, $-(CH_2)_pNR^eS(O)_2NR^cR^d$, $-(CH_2)_pCOR^b$, $-(CH_2)_pCSR^b$, $-(CH_2)_pS(O)R^b$, $-(CH_2)_pS(O)(NH)R^b$, $-(CH_2)_pS(O)_2R^b$, $-(CH_2)_pS(O)_2NR^cR^d$, $-(CH_2)_pSO_2OR^b$, $-(CH_2)_pCO_2R^b$, $-(CH_2)_pCONR^cR^d$, $-(CH_2)_pCSNR^cR^d$, $-(CH_2)_pOR^b$, $-(CH_2)_pSR^b$, $-(CH_2)_pCR^b(OH)$-R^e, $-(CH_2)_p$-C=NOR^b, $-O-(CH_2)_n-O-$, $-O-(CH_2)_n-CH_2-$, $-O-CH=CH-$ or $-(CH_2)_{n+2}-$, whereby n = 1 or 2, and the terminal oxygen atoms and/or carbon atoms are linked to directly adjacent ring-carbon atoms,

M means C_1-C_6-alkyl or a group $-COR^b$, CO_2R^b, $-O-R^b$, or $-NR^cR^d$, whereby

R^b means a hydrogen or a C_1-C_6-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkinyl, C_3-C_{10}-cycloalkyl, C_6-C_{12}-aryl or C_1-C_3-perfluoroalkyl and

R^c and R^d, independently of one another, mean a hydrogen, C_1-C_6-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkinyl, C_3-C_{10}-cycloalkyl, C_6-C_{12}-aryl, $C(O)R^b$ or a hydroxy group, whereby if

R^c is a hydroxy group, R^d can be only one hydrogen, a C_1-C_6-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkinyl, C_3-C_{10}-cycloalkyl or C_6-C_{12}-aryl and vice versa, and

R^e means a hydrogen, C_1-C_6-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkinyl, C_3-C_{10}-cycloalkyl or C_6-C_{12}-aryl, and

p can be a number from 0- 6,

or

R^3 is a radical C = C-R^gR^h, whereby

R^g and R^h, independently of one another, are a hydrogen or a C_1-C_8-alkyl, C_2-C_8-alkenyl or C_2-C_8-alkinyl that optionally is substituted in one or more places, in the same way or differently, with X, in which

X is a cyano, halogen, hydroxy, nitro, $-C(O)R^b$, CO_2R^b, $-O-R^b$, $-C(O)-NR^cR^d$, $-NR^cR^d$ with the meanings, already further mentioned above, for R^b, R^c and R^d, and

R^{4a} and R^{4b}, independently of one another, mean a hydrogen atom, a C_1-C_4-alkyl, a C_2-C_4-alkenyl or together with the ring-carbon atom forming a 3- to 6-membered ring,

A means a monocyclic or bicyclic, carbocyclic or heterocyclic aromatic ring, which optionally can be substituted in one or more places with C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkinyl, C_1-C_6-perfluoroalkyl, C_1-C_6-

perfluoroalkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkoxy, $(CH_2)_p$-C_3-C_{10}-cycloalkyl, $(CH_2)_p$-heterocycloalkyl, $(CH_2)_pCN$, $(CH_2)_pHal$, $(CH_2)_pNO_2$, $(CH_2)_p$-C_6-C_{12}-aryl, $(CH_2)_p$-heteroaryl, $-(CH_2)_pPO_3(R^b)_2$, $-(CH_2)_pNR^cR^d$, $-(CH_2)_pNR^eCOR^b$, $-(CH_2)_pNR^eCSR^b$, $-(CH_2)_pNR^eS(O)R^b$, $-(CH_2)_pNR^eS(O)_2R^b$, $-(CH_2)_pNR^eCONR^cR^d$, $-(CH_2)_pNR^eCOOR^b$, $-(CH_2)_pNR^eC(NH)NR^cR^d$, $-(CH_2)_pNR^eCSNR^cR^d$, $-(CH_2)_pNR^eS(O)NR^cR^d$, $-(CH_2)_pNR^eS(O)_2NR^cR^d$, $-(CH_2)_pCOR^b$, $-(CH_2)_pCSR^b$, $-(CH_2)_p$ $S(O)R^b$, $-(CH_2)_pS(O)(NH)R^b$, $-(CH_2)_pS(O)_2R^b$, $-(CH_2)_pS(O)_2NR^cR^d$, $-(CH_2)_pSO_2OR^b$, $-(CH_2)_pCO_2R^b$, $-(CH_2)_pCONR^cR^d$, $-(CH_2)_pCSNR^cR^d$, $-(CH_2)_pOR^b$, $-(CH_2)_pSR^b$, $-(CH_2)_pCR^b(OH)$-R^d, $-(CH_2)_p$-C=NOR^b, -O-$(CH_2)_n$-O-, -O-$(CH_2)_n$-CH_2-, -O-CH=CH- or $-(CH_2)_{n+2}$-, whereby n = 1 or 2, and the terminal oxygen atoms and/or carbon atoms are linked to directly adjacent ring-carbon atoms, or

A means a radical $-CO_2R^b$, $C(O)NR^cR^d$, COR^b,

or

A means an alkenyl group $-CR^5 = CR^6R^7$, whereby

R^5, R^6 and R^7 are the same or different and, independently of one another, mean hydrogen atoms, halogen atoms, aryl radicals or an unsubstituted or partially or completely fluorinated C_1-C_5–alkyl group, or

A means an alkinyl group $-C{\equiv}CR^5$, with the meaning cited above for R^5, and

B means a carbonyl group or a CH_2 group

as well as their pharmaceutically acceptable salts.

2. Compounds according to claim 1, in which R^1 and R^2 preferably mean a hydrogen atom, a methyl group or an ethyl group.

3. Compounds according to claim 1, in which R^1 and R^2 preferably together with the C atom of the chain form a ring with a total of 3 to 7 links.

4. Compounds according to claims 1 to 3, in which R^3 preferably means alkenyl, alkinyl, arylalkinyl, heteroarylalkinyl, cycloalkylalkinyl, or heterocycloalkylalkinyl.

5. Compounds according to one of the preceding claims, in which R^3 preferably means a vinyl, ethinyl, propinyl, butinyl, pentinyl, hexinyl, heptinyl, octinyl, hydroxypropinyl, hydroxybutinyl, 3-hydroxy-3-methylbutinyl, hydroxypentinyl, carboxypropinyl, t-butylcarboxypropinyl, phenylethinyl, (hydroxyphenyl)ethinyl, (methoxyphenyl)ethinyl, (dimethylaminophenyl)ethinyl, (methylphenyl)ethinyl, (cyanophenyl)ethinyl, (trifluoromethyl)ethinyl, (diphenyl)ethinyl, (nitrophenyl)ethinyl, (tert-butylphenyl)ethinyl, (acetylphenyl)ethinyl, (acetoxyphenyl)ethinyl, (carboxyphenyl)ethinyl or a benzylethinyl group.

6. Compounds according to one of the preceding claims, in which A is preferably an aromatic ring.

7. Compounds according to one of the preceding claims, in which A is preferably a phenyl or naphthyl radical.

8. Compounds according to claim 7, in which A preferably is an unsubstituted phenyl radical or optionally a phenyl radical that is substituted in one or more places.

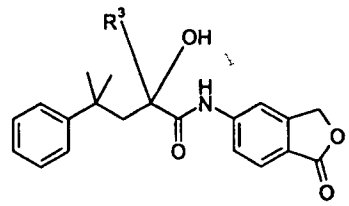
9. Compounds according to claim 8, whereby the phenyl radical is preferably substituted with one or two halogen atoms or a trifluoromethyl group.

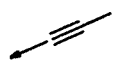
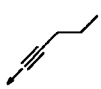
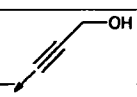
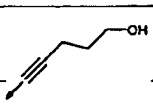
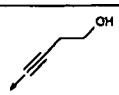
10. Compounds according to claim 9, in which the halogen atoms are preferably chlorine and/or fluorine.

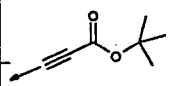
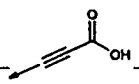
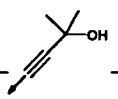
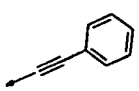
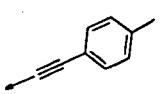
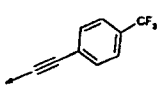
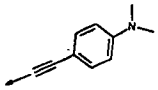
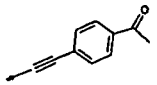
11. Compounds according to claims 1-8, in which A preferably is an $-O-(CH_2)_n-O-$ or $-O-(CH_2)_n-CH_2-$substituted phenyl ring, whereby the respectively directly adjacent ring-carbon atoms are linked.

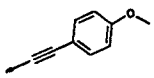
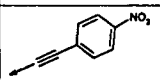
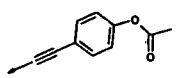
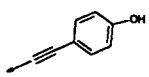
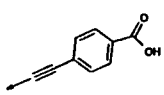
12. Compounds according to one of the preceding claims, in which R^{4a} and R^{4b}, independently of one another, in each case are a hydrogen atom.

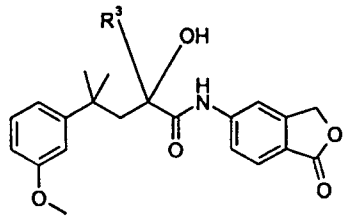
13. Compounds according to claims 1 to 12, namely:

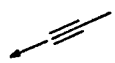
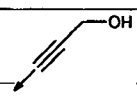
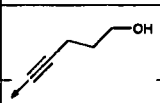
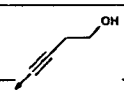


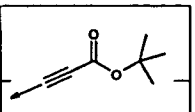
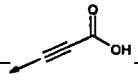
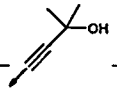
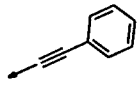
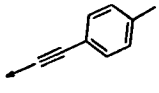
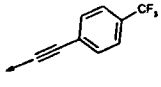
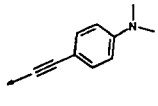
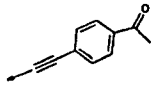
No.	Racemic or Enantiomer	R3
1	rac	
2	+	
3	-	
4	rac	
5	+	
6	-	
7	rac	
8	+	
9	-	
10	rac	
11	+	
12	-	
13	rac	
14	+	
15	-	
16	rac	
17	+	
18	-	
19	rac	

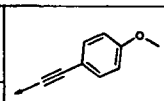
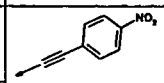
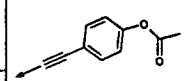
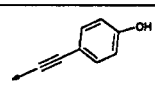
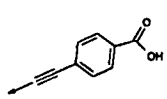
20	+	
21	-	
22	rac	
23	+	
24	-	
25	rac	
26	+	
27	-	
28	rac	
29	+	
30	-	
31	rac	
32	+	
33	-	
34	rac	
35	+	
36	-	
37	rac	
38	+	
39	-	
40	rac	
41	+	
42	-	
43	rac	

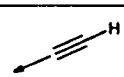
44	+	
45	-	
46	rac	
47	+	
48	-	
49	rac	
50	+	
51	-	
52	rac	
53	+	
54	-	
55	rac	
56	+	
57	-	
58	rac	
59	+	
60	-	

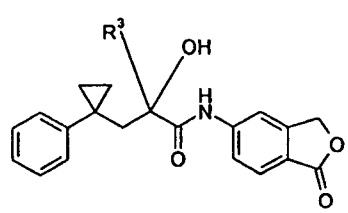


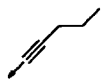
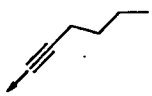
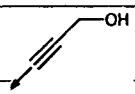
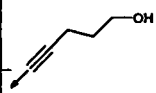
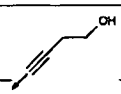
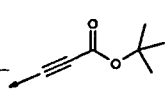
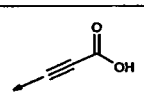
No.	Racemic or Enantiomer	R3
61	rac	
62	+	
63	-	
64	rac	
65	+	
66	-	
67	rac	
68	+	
69	-	
70	rac	
71	+	
72	-	
73	rac	
74	+	
75	-	
76	rac	
77	+	
78	-	
79	rac	
80	+	
81	-	

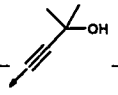
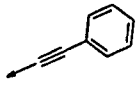
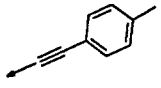
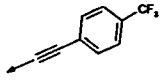
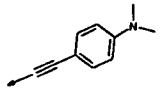
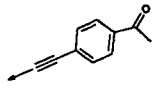
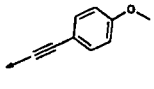
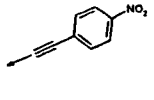
82	rac	
83	+	
84	-	
85	rac	
86	+	
87	-	
88	rac	
89	+	
90	-	
91	rac	
92	+	
93	-	
94	rac	
95	+	
96	-	
97	rac	
98	+	
99	-	
100	rac	
101	+	
102	-	
103	rac	
104	+	
105	-	

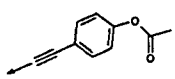
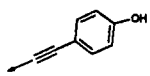
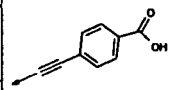
106	rac	
107	+	
108	-	
109	rac	
110	+	
111	-	
112	rac	
113	+	
114	-	
115	rac	
116	+	
117	-	
118	rac	
119	+	
120	-	

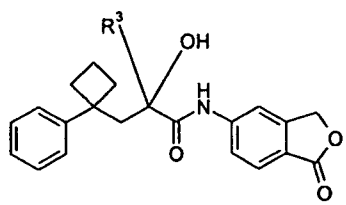
No.	Racemic or Enantiomer	R3
121	rac	
122	+	
123	-	
124	rac	

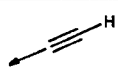
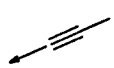
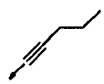


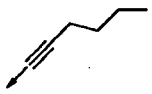
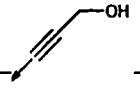
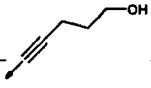
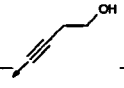
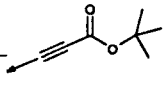
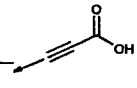
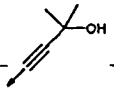
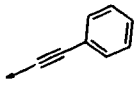
125	+	
126	-	
127	rac	
128	+	
129	-	
130	rac	
131	+	
132	-	
133	rac	
134	+	
135	-	
136	rac	
137	+	
138	-	
139	rac	
140	+	
141	-	
142	rac	
143	+	
144	-	
145	rac	
146	+	

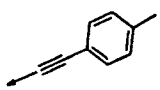
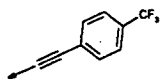
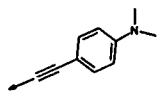
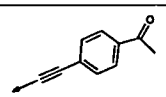
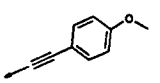
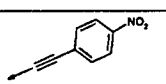
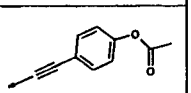
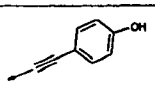
147	-	
148	rac	
149	+	
150	-	
151	rac	
152	+	
153	-	
154	rac	
155	+	
156	-	
157	rac	
158	+	
159	-	
160	rac	
161	+	
162	-	
163	rac	
164	+	
165	-	
166	rac	
167	+	
168	-	
169	rac	
170	+	

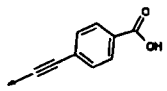
171	-	
172	rac	
173	+	
174	-	
175	rac	
176	+	
177	-	
178	rac	
179	+	
180	-	

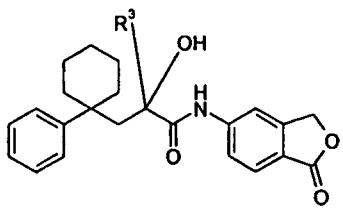


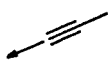
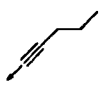
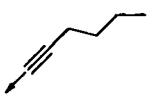
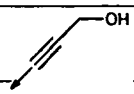
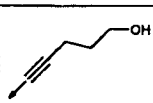
No.	Racemic or Enantiomer	R3
181	rac	
182	+	
183	-	
184	rac	
185	+	
186	-	
187	rac	
188	+	
189	-	

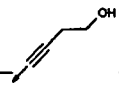
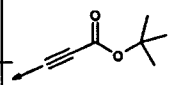
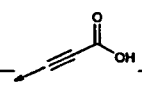
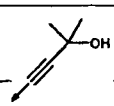
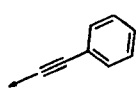
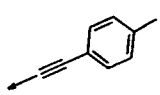
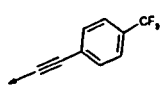
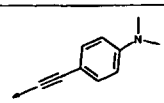
190	rac	
191	+	
192	-	
193	rac	
194	+	
195	-	
196	rac	
197	+	
198	-	
199	rac	
200	+	
201	-	
202	rac	
203	+	
204	-	
205	rac	
206	+	
207	-	
208	rac	
209	+	
210	-	
211	rac	
212	+	
213	-	

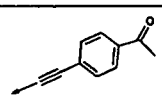
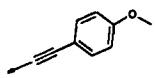
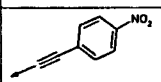
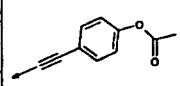
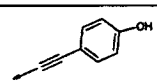
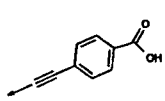
214	rac	
215	+	
216	-	
217	rac	
218	+	
219	-	
220	rac	
221	+	
222	-	
223	rac	
224	+	
225	-	
226	rac	
227	+	
228	-	
229	rac	
230	+	
231	-	
232	rac	
233	+	
234	-	
235	rac	
236	+	
237	-	

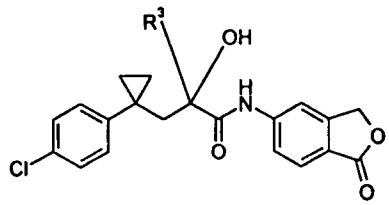
238	rac	
239	+	
240	-	

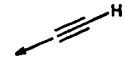
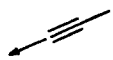
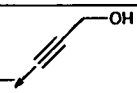
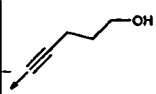
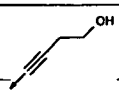
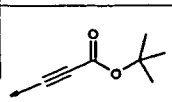


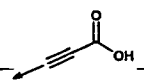
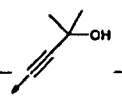
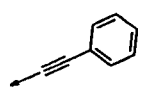
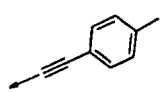
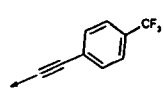
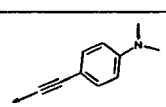
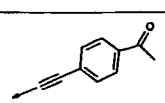
No.	Racemic or Enantiomer	R3
241	rac	
242	+	
243	-	
244	rac	
245	+	
246	-	
247	rac	
248	+	
249	-	
250	rac	
251	+	
252	-	
253	rac	
254	+	
255	-	
256	rac	

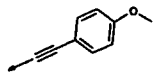
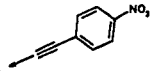
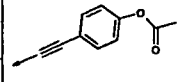
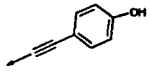
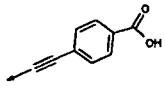
257	+	
258	-	
259	rac	
260	+	
261	-	
262	rac	
263	+	
264	-	
265	rac	
266	+	
267	-	
268	rac	
269	+	
270	-	
271	rac	
272	+	
273	-	
274	rac	
275	+	
276	-	
277	rac	
278	+	
279	-	
280	rac	

281	+	
282	-	
283	rac	
284	+	
285	-	
286	rac	
287	+	
288	-	
289	rac	
290	+	
291	-	
292	rac	
293	+	
294	-	
295	rac	
296	+	
297	-	
298	rac	
299	+	
300	-	

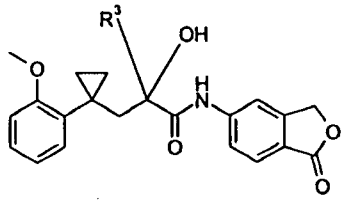


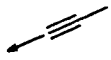
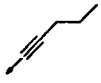
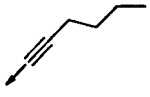
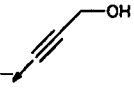
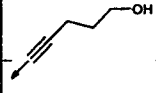
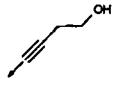
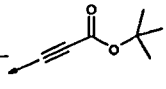
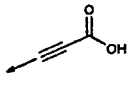
No.	Racemic or Enantiomer	R3
301	rac	
302	+	
303	-	
304	rac	
305	+	
306	-	
307	rac	
308	+	
309	-	
310	rac	
311	+	
312	-	
313	rac	
314	+	
315	-	
316	rac	
317	+	
318	-	
319	rac	
320	+	
321	-	
322	rac	

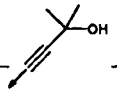
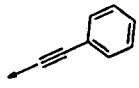
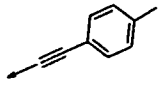
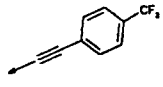
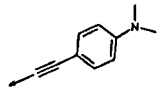
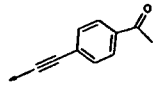
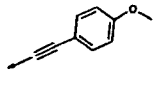
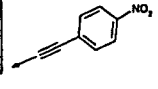
323	+	
324	-	
325	rac	
326	+	
327	-	
328	rac	
329	+	
330	-	
331	rac	
332	+	
333	-	
334	rac	
335	+	
336	-	
337	rac	
338	+	
339	-	
340	rac	
341	+	
342	-	
343	rac	
344	+	

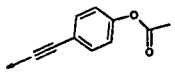
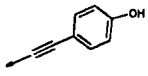
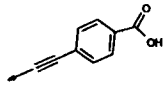
345	-	
346	rac	
347	+	
348	-	
349	rac	
350	+	
351	-	
352	rac	
353	+	
354	-	
355	rac	
356	+	
357	-	
358	rac	
359	+	
360	-	

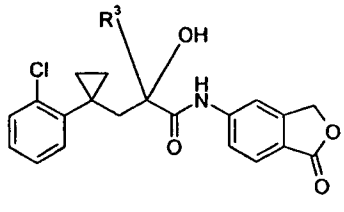
No.	Racemic or Enantiomer	R3
361	rac	
362	+	
363	-	

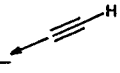
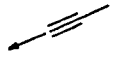


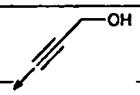
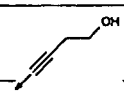
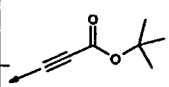
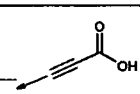
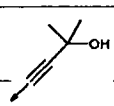
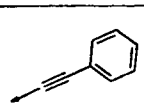
364	rac	
365	+	
366	-	
367	rac	
368	+	
369	-	
370	rac	
371	+	
372	-	
373	rac	
374	+	
375	-	
376	rac	
377	+	
378	-	
379	rac	
380	+	
381	-	
382	rac	
383	+	
384	-	
385	rac	

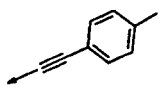
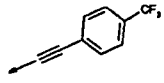
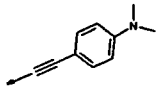
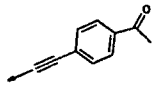
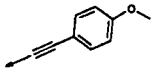
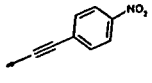
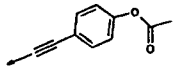
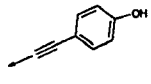
386	+	
387	-	
388	rac	
389	+	
390	-	
391	rac	
392	+	
393	-	
394	rac	
395	+	
396	-	
397	rac	
398	+	
399	-	
400	rac	
401	+	
402	-	
403	rac	
404	+	
405	-	
406	rac	
407	+	
408	-	
409	rac	

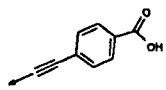
410	+	
411	-	
412	rac	
413	+	
414	-	
415	rac	
416	+	
417	-	
418	rac	
419	+	
420	-	

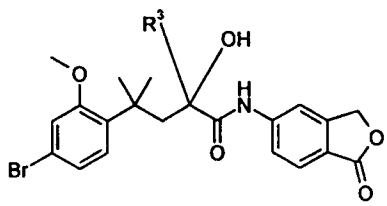


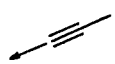
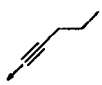
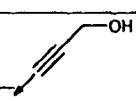
No.	Racemic or Enantiomer	R3
421	rac	
422	+	
423	-	
424	rac	
425	+	
426	-	
427	rac	
428	+	
429	-	

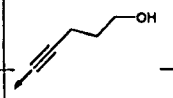
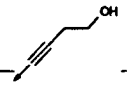
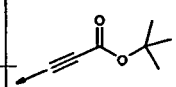
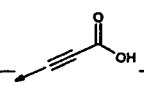
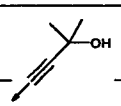
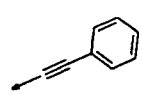
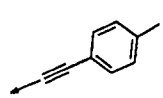
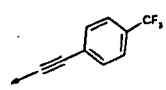
430	rac	
431	+	
432	-	
433	rac	
434	+	
435	-	
436	rac	
437	+	
438	-	
439	rac	
440	+	
441	-	
442	rac	
443	+	
444	-	
445	rac	
446	+	
447	-	
448	rac	
449	+	
450	-	
451	rac	
452	+	
453	-	

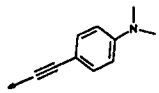
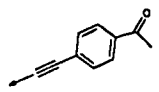
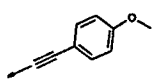
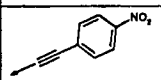
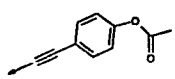
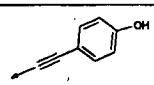
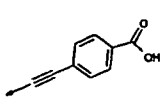
454	rac	
455	+	
456	-	
457	rac	
458	+	
459	-	
460	rac	
461	+	
462	-	
463	rac	
464	+	
465	-	
466	rac	
467	+	
468	-	
469	rac	
470	+	
471	-	
472	rac	
473	+	
474	-	
475	rac	
476	+	
477	-	

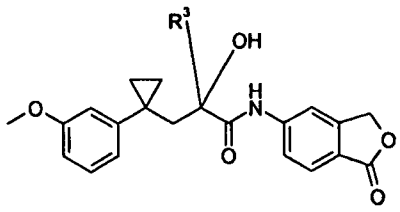
478	rac	
479	+	
480	-	

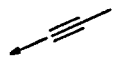
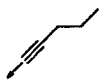
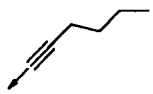
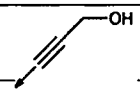
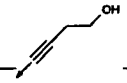
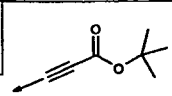


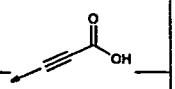
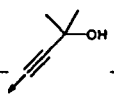
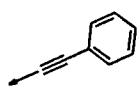
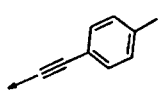
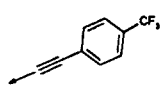
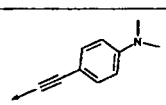
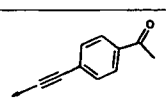
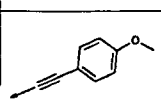
No.	Racemic or Enantiomer	R3
481	rac	
482	+	
483	-	
484	rac	
485	+	
486	-	
487	rac	
488	+	
489	-	
490	rac	
491	+	
492	-	
493	rac	
494	+	

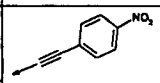
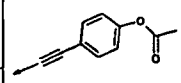
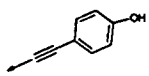
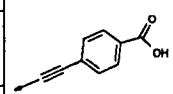
495	-	
496	rac	
497	+	
498	-	
499	rac	
500	+	
501	-	
502	rac	
503	+	
504	-	
505	rac	
506	+	
507	-	
508	rac	
509	+	
510	-	
511	rac	
512	+	
513	-	
214	rac	
515	+	
516	-	
517	rac	
518	+	

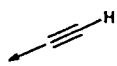
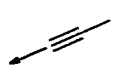
519	-	
520	rac	
521	+	
522	-	
523	rac	
524	+	
525	-	
526	rac	
227	+	
528	-	
529	rac	
530	+	
531	-	
532	rac	
533	+	
534	-	
535	rac	
536	+	
537	-	
538	rac	
539	+	
540	-	

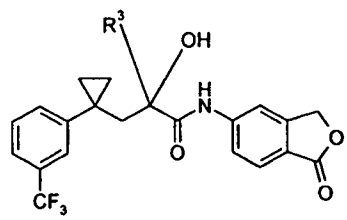


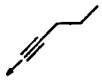
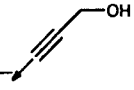
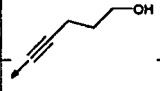
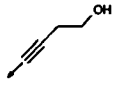
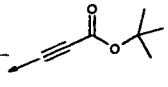
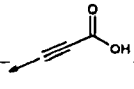
No.	Racemic or Enantiomer	R3
541	rac	
542	+	
543	-	
544	rac	
545	+	
546	-	
547	rac	
548	+	
549	-	
550	rac	
551	+	
552	-	
553	rac	
554	+	
555	-	
556	rac	
557	+	
558	-	
559	rac	
560	+	
561	-	
562	rac	

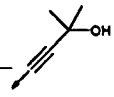
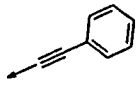
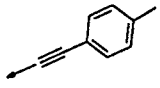
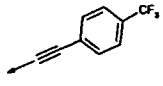
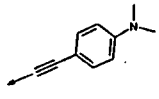
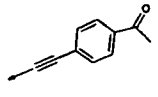
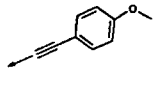
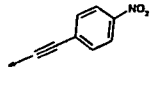
563	+	
564	-	
565	rac	
566	+	
567	-	
568	rac	
569	+	
570	-	
571	rac	
572	+	
573	-	
574	rac	
575	+	
576	-	
577	rac	
578	+	
579	-	
580	rac	
581	+	
582	-	
583	rac	
584	+	
585	-	
586	rac	

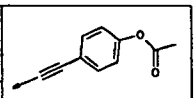
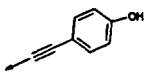
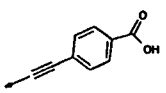
587	+	
588	-	
589	rac	
590	+	
591	-	
592	rac	
593	+	
594	-	
595	rac	
596	+	
597	-	
598	rac	
599	+	
600	-	

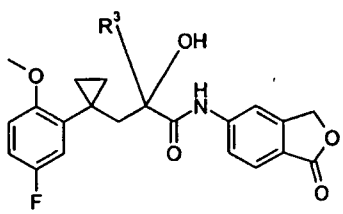
No.	Racemic or Enantiomer	R3
601	rac	
602	+	
603	-	
604	rac	
605	+	

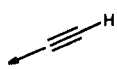
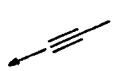
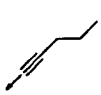
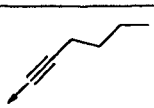


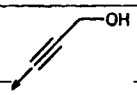
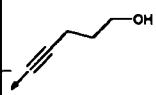
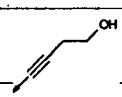
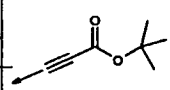
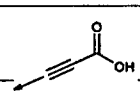
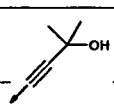
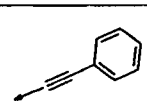
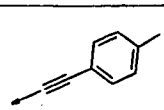
606	-	
607	rac	
608	+	
609	-	
610	rac	
611	+	
612	-	
613	rac	
614	+	
615	-	
616	rac	
617	+	
618	-	
619	rac	
620	+	
621	-	
622	rac	
623	+	
624	-	
625	rac	
626	+	
627	-	

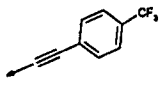
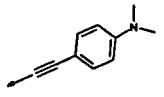
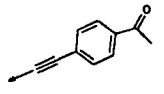
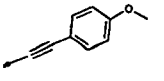
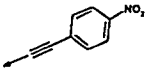
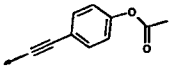
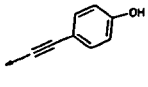
628	rac	
629	+	
630	-	
631	rac	
632	+	
633	-	
634	rac	
635	+	
636	-	
637	rac	
638	+	
639	-	
640	rac	
641	+	
642	-	
643	rac	
644	+	
645	-	
646	rac	
647	+	
648	-	
649	rac	
650	+	
651	-	

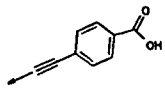
652	rac	
653	+	
654	-	
655	rac	
656	+	
657	-	
658	rac	
659	+	
660	-	

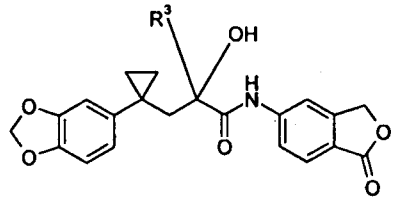


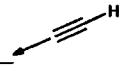
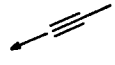
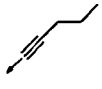
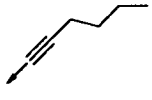
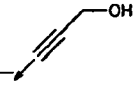
No.	Racemic or Enantiomer	R3
661	rac	
662	+	
663	-	
664	rac	
665	+	
666	-	
667	rac	
668	+	
669	-	
670	rac	

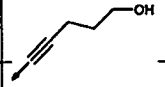
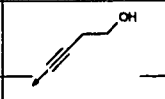
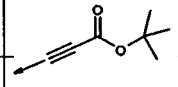
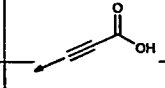
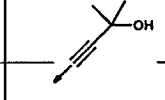
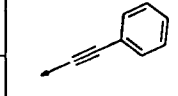
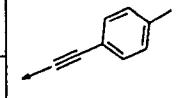
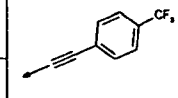
671	+	
672	-	
673	rac	
674	+	
675	-	
676	rac	
677	+	
678	-	
679	rac	
680	+	
681	-	
682	rac	
683	+	
684	-	
685	rac	
686	+	
687	-	
688	rac	
689	+	
690	-	
691	rac	
692	+	
693	-	
694	rac	

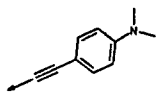
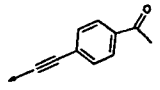
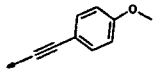
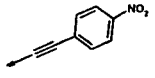
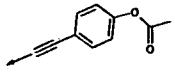
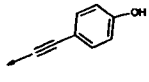
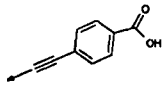
695	+	
696	-	
697	rac	
698	+	
699	-	
700	rac	
701	+	
702	-	
703	rac	
704	+	
705	-	
706	rac	
707	+	
708	-	
709	rac	
710	+	
711	-	
712	rac	
713	+	
714	-	
715	rac	
716	+	

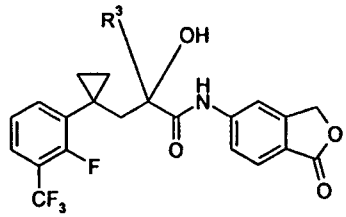
717	-	
718	rac	
719	+	
720	-	

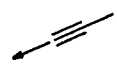
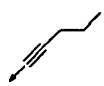
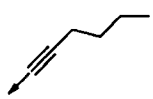
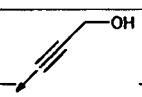
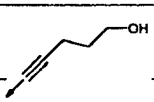


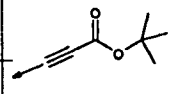
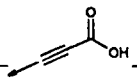
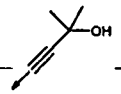
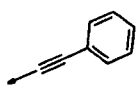
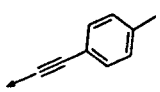
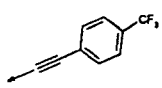
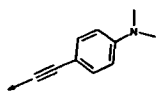
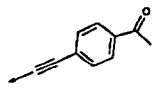
No.	Racemic or Enantiomer	R3
721	rac	
722	+	
723	-	
724	rac	
725	+	
726	-	
727	rac	
728	+	
729	-	
730	rac	
731	+	
732	-	
733	rac	
734	+	
735	-	

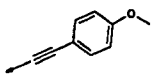
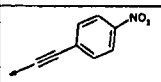
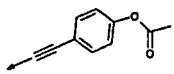
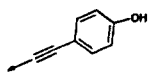
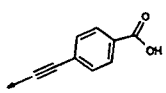
736	rac	
737	+	
738	-	
739	rac	
740	+	
741	-	
742	rac	
743	+	
744	-	
745	rac	
746	+	
747	-	
748	rac	
749	+	
750	-	
751	rac	
752	+	
753	-	
754	rac	
755	+	
756	-	
757	rac	
758	+	
759	-	

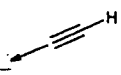
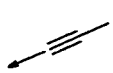
760	rac	
761	+	
762	-	
763	rac	
764	+	
765	-	
766	rac	
767	+	
768	-	
769	rac	
770	+	
771	-	
772	rac	
773	+	
774	-	
775	rac	
776	+	
777	-	
778	rac	
779	+	
780	-	

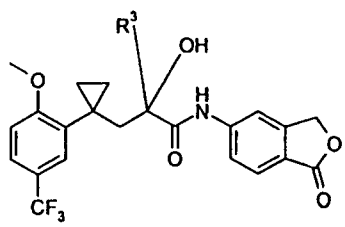


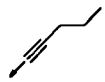
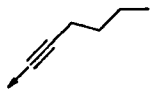
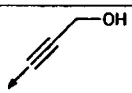
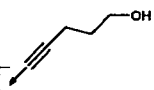
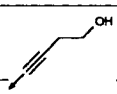
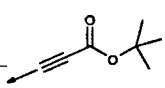
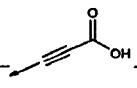
No.	Racemic or Enantiomer	R3
781	rac	
782	+	
783	-	
784	rac	
785	+	
786	-	
787	rac	
788	+	
789	-	
790	rac	
791	+	
792	-	
793	rac	
794	+	
795	-	
796	rac	
797	+	
798	-	
799	rac	
800	+	
801	-	

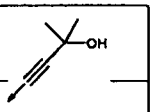
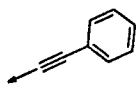
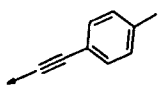
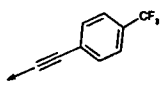
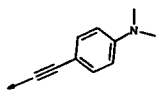
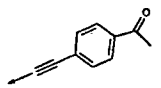
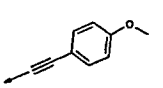
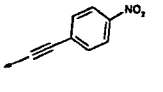
802	rac	
803	+	
804	-	
805	rac	
806	+	
807	-	
808	rac	
809	+	
810	-	
811	rac	
812	+	
813	-	
814	rac	
815	+	
816	-	
817	rac	
818	+	
819	-	
820	rac	
821	+	
822	-	
823	rac	
824	+	
825	-	

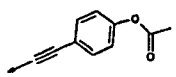
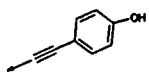
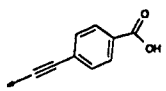
826	rac	
827	+	
828	-	
829	rac	
830	+	
831	-	
832	rac	
833	+	
834	-	
835	rac	
836	+	
837	-	
838	rac	
839	+	
840	-	

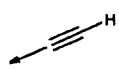
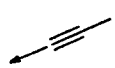
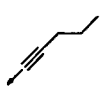
No.	Racemic or Enantiomer	R3
841	rac	
842	+	
843	-	
844	rac	

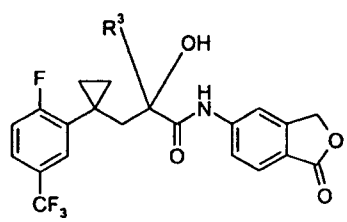


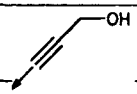
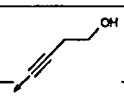
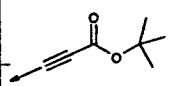
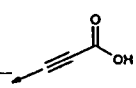
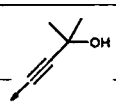
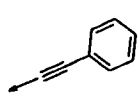
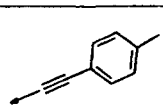
845	+	
846	-	
847	rac	
848	+	
849	-	
850	rac	
851	+	
852	-	
853	rac	
854	+	
855	-	
856	rac	
857	+	
858	-	
859	rac	
860	+	
861	-	
862	rac	
863	+	
864	-	
865	rac	
866	+	
867	-	

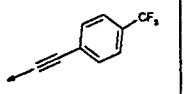
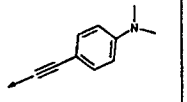
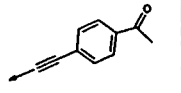
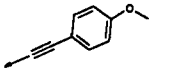
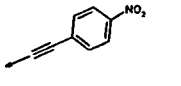
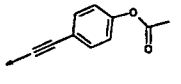
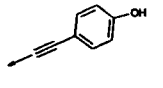
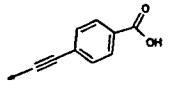
868	rac	
869	+	
870	-	
871	rac	
872	+	
873	-	
874	rac	
875	+	
876	-	
877	rac	
878	+	
879	-	
880	rac	
881	+	
882	-	
883	rac	
884	+	
885	-	
886	rac	
887	+	
888	-	
889	rac	
890	+	
891	-	

892	rac	
893	+	
894	-	
895	rac	
896	+	
897	-	
898	rac	
899	+	
900	-	

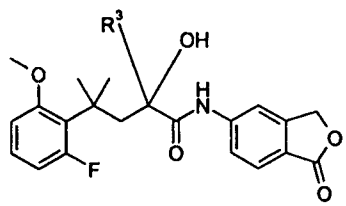
No.	Racemic or Enantiomer	R3
901	rac	
902	+	
903	-	
904	rac	
905	+	
906	-	
907	rac	
908	+	
909	-	
910	rac	

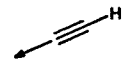
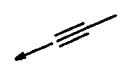
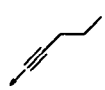
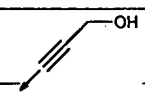
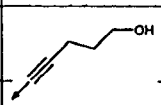


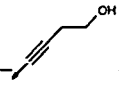
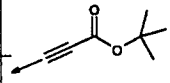
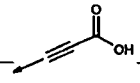
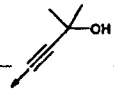
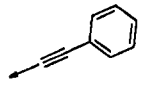
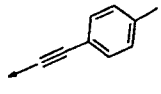
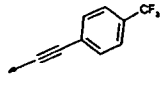
911	+	
912	-	
913	rac	
914	+	
915	-	
916	rac	
917	+	
918	-	
919	rac	
920	+	
921	-	
922	rac	
923	+	
924	-	
925	rac	
926	+	
927	-	
928	rac	
929	+	
930	-	
931	rac	
932	+	
933	-	
934	rac	

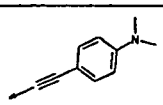
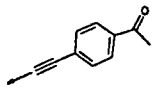
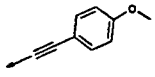
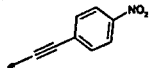
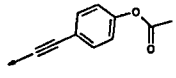
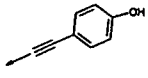
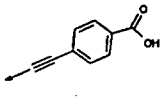
935	+	
936	-	
937	rac	
938	+	
939	-	
940	rac	
941	+	
942	-	
943	rac	
944	+	
945	-	
946	rac	
947	+	
948	-	
949	rac	
950	+	
951	-	
952	rac	
953	+	
954	-	
955	rac	
956	+	
957	-	
958	rac	

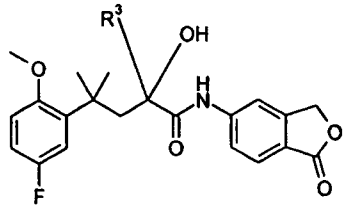
959	+	
960	-	

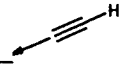
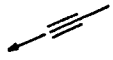
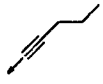
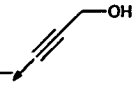
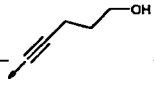
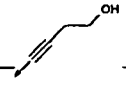


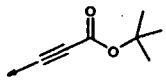
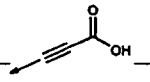
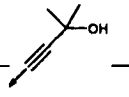
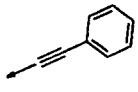
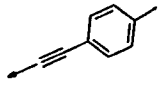
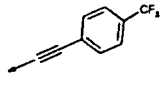
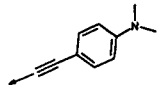
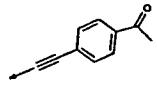
No.	Racemic or Enantiomer	R3
961	rac	
962	+	
963	-	
964	rac	
965	+	
966	-	
967	rac	
968	+	
969	-	
970	rac	
971	+	
972	-	
973	rac	
974	+	
975	-	
976	rac	
977	+	

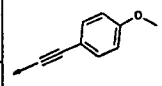
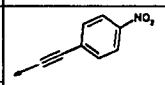
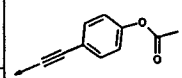
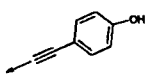
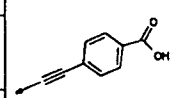
978	-	
979	rac	
980	+	
981	-	
982	rac	
983	+	
984	-	
985	rac	
986	+	
987	-	
988	rac	
989	+	
990	-	
991	rac	
992	+	
993	-	
994	rac	
995	+	
996	-	
997	rac	
998	+	
999	-	

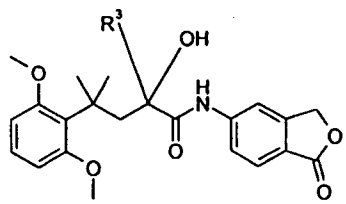
1000	rac	
1001	+	
1002	-	
1003	rac	
1004	+	
1005	-	
1006	rac	
1007	+	
1008	-	
1009	rac	
1010	+	
1011	-	
1012	rac	
1013	+	
1014	-	
1015	rac	
1016	+	
1017	-	
1018	rac	
1019	+	
1020	-	

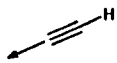


No.	Racemic or Enantiomer	R3
1021	rac	
1022	+	
1023	-	
1024	rac	
1025	+	
1026	-	
1027	rac	
1028	+	
1029	-	
1030	rac	
1031	+	
1032	-	
1033	rac	
1034	+	
1035	-	
1036	rac	
1037	+	
1038	-	
1039	rac	
1040	+	
1041	-	

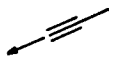
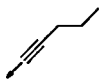
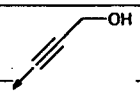
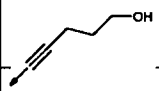
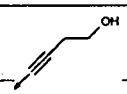
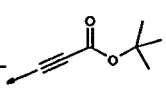
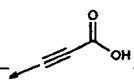
1042	rac	
1043	+	
1044	-	
1045	rac	
1046	+	
1047	-	
1048	rac	
1049	+	
1050	-	
1051	rac	
1052	+	
1053	-	
1054	rac	
1055	+	
1056	-	
1057	rac	
1058	+	
1059	-	
1060	rac	
1061	+	
1062	-	
1063	rac	
1064	+	

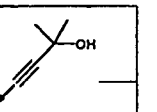
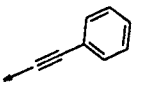
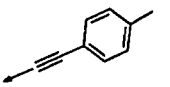
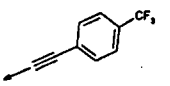
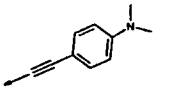
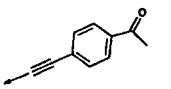
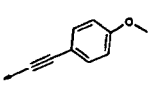
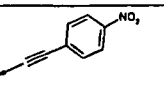
1065	-	
1066	rac	
1067	+	
1068	-	
1069	rac	
1070	+	
1071	-	
1072	rac	
1073	+	
1074	-	
1075	rac	
1076	+	
1077	-	
1078	rac	
1079	+	
1080	-	

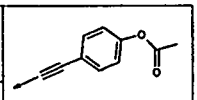
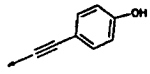
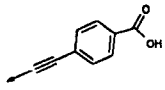


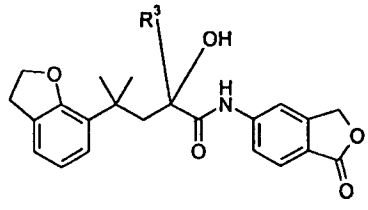
No.	Racemic or Enantiomer	R3
1081	rac	
1082	+	
1083	-	

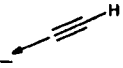
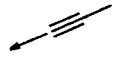
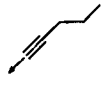
149

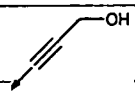
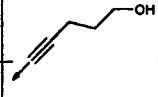
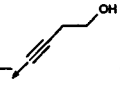
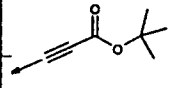
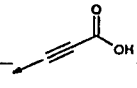
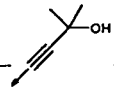
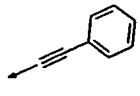
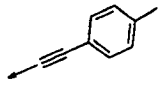
1084	rac	
1085	+	
1086	-	
1087	rac	
1088	+	
1089	-	
1090	rac	
1091	+	
1092	-	
1093	rac	
1094	+	
1095	-	
1096	rac	
1097	+	
1098	-	
1099	rac	
1100	+	
1101	-	
1102	rac	
1103	+	
1104	-	
1105	rac	
1106	+	
1107	-	

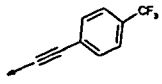
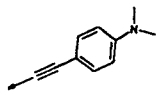
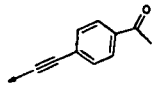
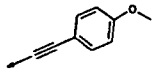
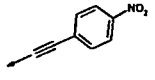
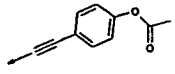
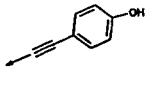
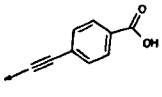
1108	rac	
1109	+	
1110	-	
1111	rac	
1112	+	
1113	-	
1114	rac	
1115	+	
1116	-	
1117	rac	
1118	+	
1119	-	
1120	rac	
1121	+	
1122	-	
1123	rac	
1124	+	
1125	-	
1126	rac	
1127	+	
1128	-	
1129	rac	
1130	+	
1131	-	

1132	rac	
1133	+	
1134	-	
1135	rac	
1136	+	
1137	-	
1138	rac	
1139	+	
1140	-	

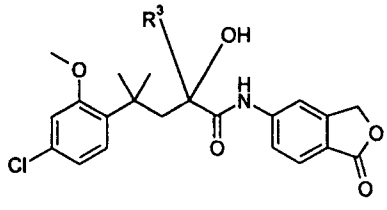


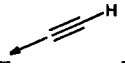
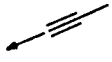
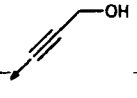
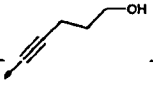
No.	Racemic or Enantiomer	R3
1141	rac	
1142	+	
1143	-	
1144	rac	
1145	+	
1146	-	
1147	rac	
1148	+	
1149	-	
1150	rac	
1151	+	

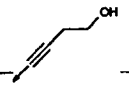
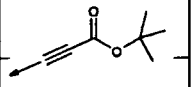
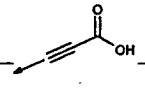
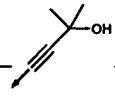
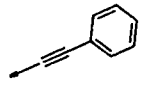
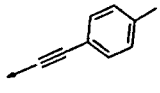
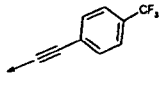
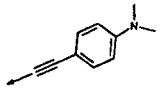
1152	-	
1153	rac	
1154	+	
1155	-	
1156	rac	
1157	+	
1158	-	
1159	rac	
1160	+	
1161	-	
1162	rac	
1163	+	
1164	-	
1165	rac	
1166	+	
1167	-	
1168	rac	
1169	+	
1170	-	
1171	rac	
1172	+	
1173	-	
1174	rac	
1175	+	

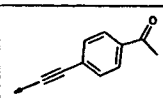
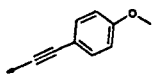
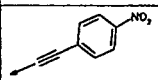
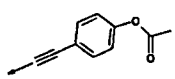
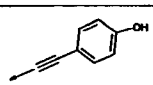
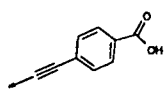
1176	-	
1177	rac	
1178	+	
1179	-	
1180	rac	
1181	+	
1182	-	
1183	rac	
1184	+	
1185	-	
1186	rac	
1187	+	
1188	-	
1189	rac	
1190	+	
1191	-	
1192	rac	
1193	+	
1194	-	
1195	rac	
1196	+	
1197	-	
1198	rac	
1199	+	

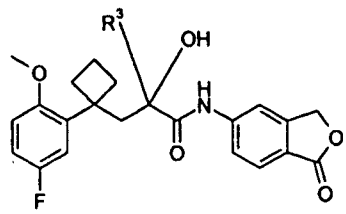
1200	-	

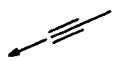
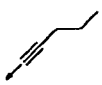
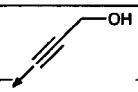
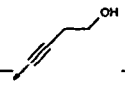


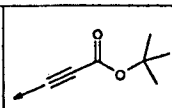
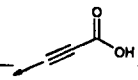
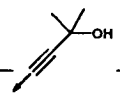
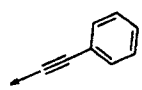
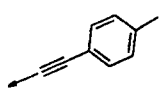
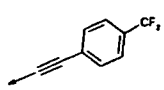
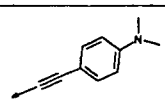
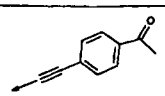
No.	Racemic or Enantiomer	R3
1201	rac	
1202	+	
1203	-	
1204	rac	
1205	+	
1206	-	
1207	rac	
1208	+	
1209	-	
1210	rac	
1211	+	
1212	-	
1213	rac	
1214	+	
1215	-	
1216	rac	
1217	+	
1218	-	

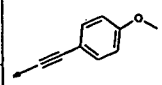
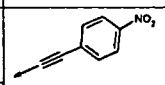
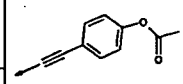
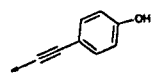
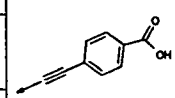
1219	rac	
1220	+	
1221	-	
1222	rac	
1223	+	
1224	-	
1225	rac	
1226	+	
1227	-	
1228	rac	
1229	+	
1230	-	
1231	rac	
1232	+	
1233	-	
1234	rac	
1235	+	
1236	-	
1237	rac	
1238	+	
1239	-	
1240	rac	

1241	+	
1242	-	
1243	rac	
1244	+	
1245	-	
1246	rac	
1247	+	
1248	-	
1249	rac	
1250	+	
1251	-	
1252	rac	
1253	+	
1254	-	
1255	rac	
1256	+	
1257	-	
1258	rac	
1259	+	
1260	-	

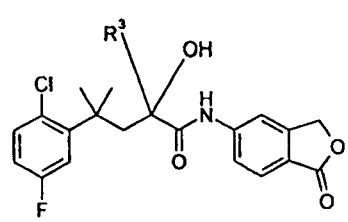


No.	Racemic or Enantiomer	R3
1261	rac	
1262	+	
1263	-	
1264	rac	
1265	+	
1266	-	
1267	rac	
1268	+	
1269	-	
1270	rac	
1271	+	
1272	-	
1273	rac	
1274	+	
1275	-	
1276	rac	
1277	+	
1278	-	
1279	rac	
1280	+	
1281	-	

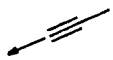
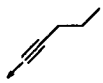
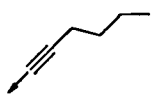
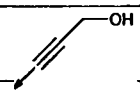
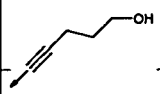
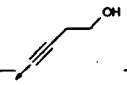
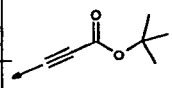
1282	rac	
1283	+	
1284	-	
1285	rac	
1286	+	
1287	-	
1288	rac	
1289	+	
1290	-	
1291	rac	
1292	+	
1293	-	
1294	rac	
1295	+	
1296	-	
1297	rac	
1298	+	
1299	-	
1300	rac	
1301	+	
1302	-	
1303	rac	

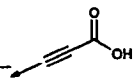
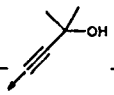
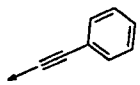
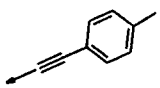
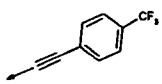
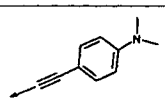
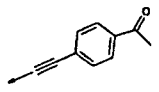
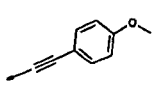
1304	+	
1305	-	
1306	rac	
1307	+	
1308	-	
1309	rac	
1310	+	
1311	-	
1312	rac	
1313	+	
1314	-	
1315	rac	
1316	+	
1317	-	
1318	rac	
1319	+	
1320	-	

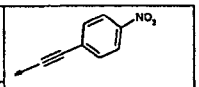
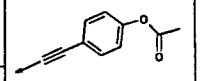
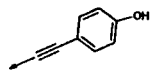
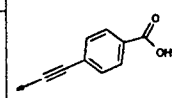
No.	Racemic or Enantiomer	R3
1321	rac	
1322	+	

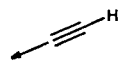


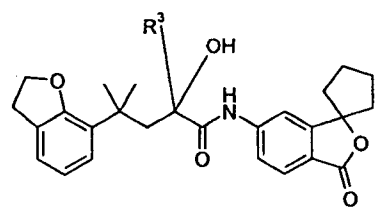
150

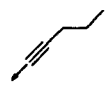
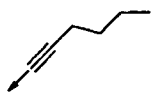
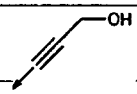
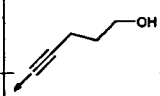
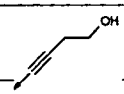
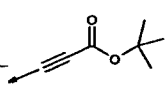
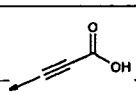
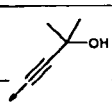
1323	-	
1324	rac	
1325	+	
1326	-	
1327	rac	
1328	+	
1329	-	
1330	rac	
1331	+	
1332	-	
1333	rac	
1334	+	
1335	-	
1336	rac	
1337	+	
1338	-	
1339	rac	
1340	+	
1341	-	
1342	rac	
1343	+	
1344	-	

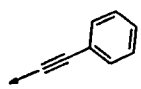
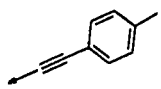
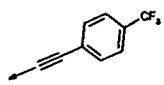
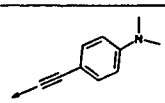
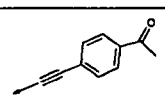
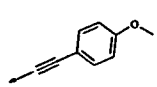
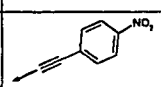
1345	rac	
1346	+	
1347	-	
1348	rac	
1349	+	
1350	-	
1351	rac	
1352	+	
1353	-	
1354	rac	
1355	+	
1356	-	
1357	rac	
1358	+	
1359	-	
1360	rac	
1361	+	
1362	-	
1363	rac	
1364	+	
1365	-	
1366	rac	
1367	+	
1368	-	

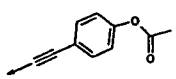
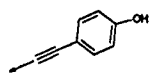
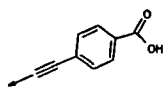
1369	rac	
1370	+	
1371	-	
1372	rac	
1373	+	
1374	-	
1375	rac	
1376	+	
1377	-	
1378	rac	
1379	+	
1380	-	

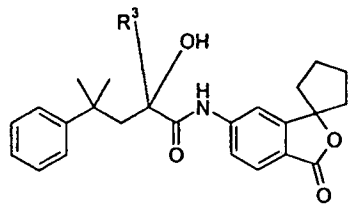
No.	Racemic or Enantiomer	R3
1381	rac	
1382	+	
1383	-	
1384	rac	
1385	+	

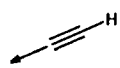
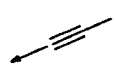


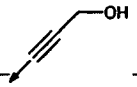
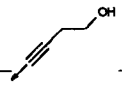
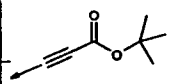
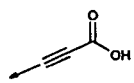
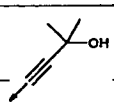
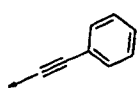
1386	-	
1387	rac	
1388	+	
1389	-	
1390	rac	
1391	+	
1392	-	
1393	rac	
1394	+	
1395	-	
1396	rac	
1397	+	
1398	-	
1399	rac	
1400	+	
1401	-	
1402	rac	
1403	+	
1404	-	
1405	rac	
1406	+	
1407	-	
1408	rac	
1409	+	

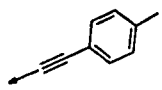
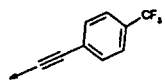
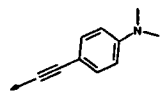
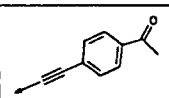
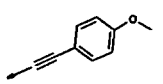
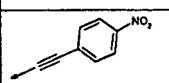
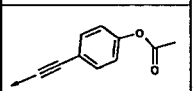
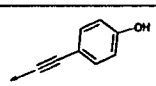
1410	-	
1411	rac	
1412	+	
1413	-	
1414	rac	
1415	+	
1416	-	
1417	rac	
1418	+	
1419	-	
1420	rac	
1421	+	
1422	-	
1423	rac	
1424	+	
1425	-	
1426	rac	
1427	+	
1428	-	
1429	rac	
1430	+	
1431	-	

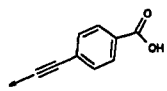
1432	rac	
1433	+	
1434	-	
1435	rac	
1436	+	
1437	-	
1438	rac	
1439	+	
1440	-	

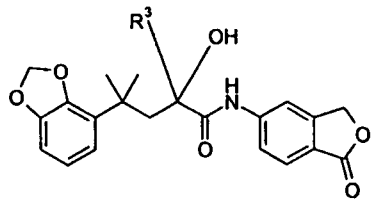


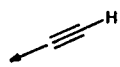
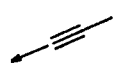
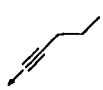
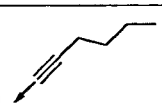
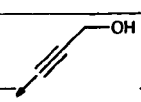
No.	Racemic or Enantiomer	R3
1441	rac	
1442	+	
1443	-	
1444	rac	
1445	+	
1446	-	
1447	rac	
1448	+	
1449	-	
1450	rac	

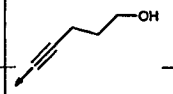
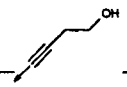
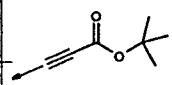
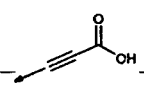
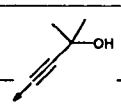
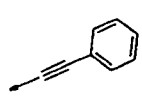
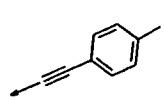
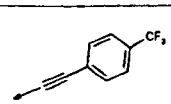
1451	+	
1452	-	
1453	rac	
1454	+	
1455	-	
1456	rac	
1457	+	
1458	-	
1459	rac	
1460	+	
1461	-	
1462	rac	
1463	+	
1464	-	
1465	rac	
1466	+	
1467	-	
1468	rac	
1469	+	
1470	-	
1471	rac	
1472	+	
1473	-	

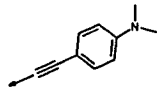
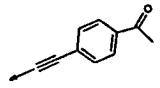
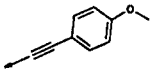
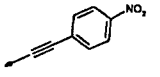
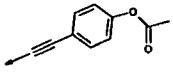
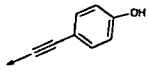
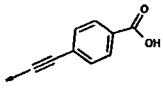
1474	rac	
1475	+	
1476	-	
1477	rac	
1478	+	
1479	-	
1480	rac	
1481	+	
1482	-	
1483	rac	
1484	+	
1485	-	
1486	rac	
1487	+	
1488	-	
1489	rac	
1490	+	
1491	-	
1492	rac	
1493	+	
1494	-	
1495	rac	
1496	+	
1497	-	

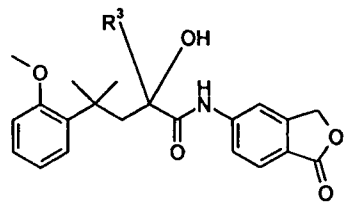
1498	rac	
1499	+	
1500	-	

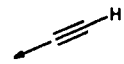
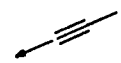
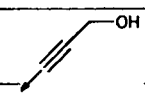
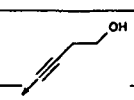
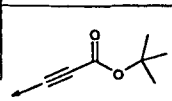


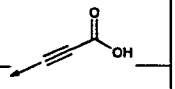
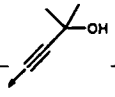
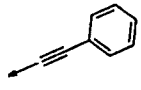
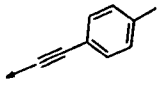
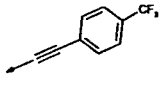
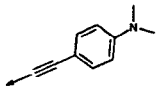
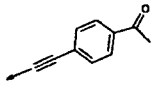
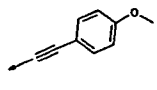
No.	Racemic or Enantiomer	R3
1501	rac	
1502	+	
1503	-	
1504	rac	
1505	+	
1506	-	
1507	rac	
1508	+	
1509	-	
1510	rac	
1511	+	
1512	-	
1513	rac	
1514	+	

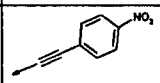
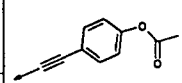
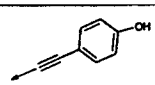
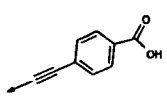
1515	-	
1516	rac	
1517	+	
1518	-	
1519	rac	
1520	+	
1521	-	
1522	rac	
1523	+	
1524	-	
1525	rac	
1526	+	
1527	-	
1528	rac	
1529	+	
1530	-	
1531	rac	
1532	+	
1533	-	
1534	rac	
1535	+	
1536	-	
1537	rac	
1538	+	

1539	-	
1540	rac	
1541	+	
1542	-	
1543	rac	
1544	+	
1545	-	
1546	rac	
1547	+	
1548	-	
1549	rac	
1550	+	
1551	-	
1552	rac	
1553	+	
1554	-	
1555	rac	
1556	+	
1557	-	
1558	rac	
1559	+	
1560	-	



No.	Racemic or Enantiomer	R3
1561	rac	
1562	+	
1563	-	
1564	rac	
1565	+	
1566	-	
1567	rac	
1568	+	
1569	-	
1570	rac	
1571	+	
1572	-	
1573	rac	
1574	+	
1575	-	
1576	rac	
1577	+	
1578	-	
1579	rac	
1580	+	
1581	-	
1582	rac	

1583	+	
1584	-	
1585	rac	
1586	+	
1587	-	
1588	rac	
1589	+	
1590	-	
1591	rac	
1592	+	
1593	-	
1594	rac	
1595	+	
1596	-	
1597	rac	
1598	+	
1599	-	
1600	rac	
1601	+	
1602	-	
1603	rac	
1604	+	
1605	-	
1606	rac	

1607	+	
1608	-	
1609	rac	
1610	+	
1611	-	
1612	rac	
1613	+	
1614	-	
1615	rac	
1616	+	
1617	-	
1618	rac	
1619	+	
1620	-	

14. Pharmaceutical composition that contains at least one compound of general formula I according to one of claims 1 to 13 and optionally at least one additional active ingredient together with pharmaceutically compatible adjuvants and/or vehicles.

15. Pharmaceutical composition according to claim 14, wherein the additional active ingredient is a SERM (selective estrogen receptor modulator), an aromatase inhibitor, an antiestrogen, or a prostaglandin.

16. Pharmaceutical composition according to claim 14, whereby the active

ingredients can be tamoxifen, 5-(4-{5-[(RS)-(4,4,5,5,5-pentafluoropentyl)sulfinyl]-pentyloxy}phenyl)-6-phenyl-8,9-dihydro-7H-benzocyclohepten-2-ol, ICI 182 780 (7alpha-[9-(4,4,5,5-pentafluoropentylsulfinyl)nonyl]estra-1,3,5(10)-triene-3,17-beta-diol), 11beta-fluoro-7alpha-[5-(methyl{3-[(4,4,5,5,5-pentafluoropentyl)sulfanyl]-propyl}amino)pentyl]estra-1,3,5(10)-triene-3,17beta-diol, 11beta-fluoro-7alpha-{5-[methyl(7,7,8,8,9,9,10,10,10-nonafluorodecyl)amino]pentyl}estra-1,3,5(10)-triene-3,17beta-diol, 11beta-fluoro-17alpha-methyl-7alpha-{5-[methyl(8,8,9,9,9-pentafluoro-nonyl)amino]pentyl}estra-1,3,5(10)-triene-3,17beta-diol, clomifene, raloxifene, fadrozole, formestane, letrozole, anastrozole or atamestane.

17. Use of compounds according to one of claims 1 to 13 for the production of a pharmaceutical agent.

18. Use of compounds according to claim 17 for the production of a pharmaceutical agent for therapy and prophylaxis of gynecological diseases such as endometriosis, leiomyomas of the uterus, dysfunctional bleeding and dysmenorrhea.

19. Use of compounds according to claim 17 for the production of a pharmaceutical agent for therapy and prophylaxis of hormone-dependent tumors.

20. Use of compounds according to claim 17 for the production of a pharmaceutical agent for therapy and prophylaxis of breast cancer.

21. Use of compounds according to claim 17 for the production of a pharmaceutical agent for therapy and prophylaxis of endometrial carcinoma.

22. Use of compounds according to claim 17 for the production of a pharmaceutical agent for therapy and prophylaxis of ovarian cancer.

23. Use of compounds according to claim 17 for the production of a pharmaceutical agent for therapy and prophylaxis of prostate cancer.

24. Use of compounds according to claim 17 for the production of a pharmaceutical agent for female hormone replacement therapy.

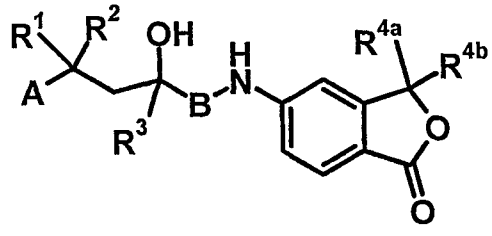
25. Use of compounds according to claim 17 for female birth control.

26. Process for the selective addition of lithium alkinyl compounds and magnesium haloalkinyl compounds to ketoamide.

AMENDED CLAIMS
received by the International Bureau on 04 October 2006 (04.10.2006)
+STATEMENT

Claims

1. Compounds of general formula I



(I),

in which

R^1 and R^2, independently of one another, mean a hydrogen atom, a straight or nonstraight, branched or unbranched C_1-C_5-alkyl group, also together with the C atom of the chain forming a ring with a total of 3-7 members,

R^3 means a radical C≡C-R^a, whereby

R^a means a hydrogen or a C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkinyl, C_3-C_{10}-cycloalkyl, or heterocycloalkyl that optionally is substituted in one or more places, in the same way or differently, with K, or an aryl or heteroaryl that optionally is substituted in one or more places, in the same way or differently, with L,

K is a cyano, halogen, hydroxy, nitro, -C(O)R^b, CO_2R^b, –O-R^b, -S-R^b, $SO_2NR^cR^d$, -C(O)-NR^cR^d, -OC(O)-NR^cR^d, or -C=NOR^b -NR^cR^d or a C_3-C_{10}-cycloalkyl that optionally is substituted in one or more places, in the same way or differently, with M, heterocycloalkyl, or aryl or heteroaryl that optionally is substituted in one or more places with L,

L means C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkinyl, C_1-C_6-

perfluoroalkyl, C_1-C_6-perfluoroalkoxy, C_1-C_6-alkoxy-C_1-C_6-alkoxy, $(CH_2)_p$-C_3-C_{10}-cycloalkyl, $(CH_2)_p$-heterocycloalkyl, $(CH_2)_pCN$, $(CH_2)_pHal$, $(CH_2)_pNO_2$, $(CH_2)_p$-C_6-C_{12}-aryl, $(CH_2)_p$-heteroaryl, $-(CH_2)_pPO_3(R^b)_2$,

$-(CH_2)_pNR^cR^d$, $-(CH_2)_pNR^eCOR^b$,

$-(CH_2)_pNR^eCSR^b$, $-(CH_2)_pNR^eS(O)R^b$,

$-(CH_2)_pNR^eS(O)_2R^b$, $-(CH_2)_pNR^eCONR^cR^d$,

$-(CH_2)_pNR^eCOOR^b$, $-(CH_2)_pNR^eC(NH)NR^cR^d$,

$-(CH_2)_pNR^eCSNR^cR^d$, $-(CH_2)_pNR^eS(O)NR^cR^d$,

$-(CH_2)_pNR^eS(O)_2NR^cR^d$, $-(CH_2)_pCOR^b$,

$-(CH_2)_pCSR^b$, $-(CH_2)_pS(O)R^b$,

$-(CH_2)_pS(O)(NH)R^b$, $-(CH_2)_pS(O)_2R^b$,

$-(CH_2)_pS(O)_2NR^cR^d$, $-(CH_2)_pSO_2OR^b$,

$-(CH_2)_pCO_2R^b$, $-(CH_2)_pCONR^cR^d$,

$-(CH_2)_pCSNR^cR^d$, $-(CH_2)_pOR^b$, $-(CH_2)_pSR^b$,

$-(CH_2)_pCR^b(OH)-R^e$, $-(CH_2)_p-C=NOR^b$,

$-O-(CH_2)_n-O-$, $-O-(CH_2)_n-CH_2-$, $-O-CH=CH-$

or $-(CH_2)_{n+2}-$, whereby n = 1 or 2, and the terminal oxygen atoms and/or carbon atoms are linked to directly adjacent ring-carbon atoms,

M means C_1-C_6-alkyl or a group $-COR^b$, CO_2R^b, $-O-R^b$, or $-NR^cR^d$, whereby

R^b means a hydrogen or a C_1-C_6-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkinyl, C_3-C_{10}-cycloalkyl, C_6-C_{12}-aryl or C_1-C_3-perfluoroalkyl and

R^c and R^d, independently of one another, mean a hydrogen,

C_1-C_6-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkinyl, C_3-C_{10}-cycloalkyl, C_6-C_{12}-aryl, $C(O)R^b$ or a hydroxy group, whereby if

R^c is a hydroxy group, R^d can be only one hydrogen, a C_1-C_6-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkinyl, C_3-C_{10}-cycloalkyl or C_6-C_{12}-aryl and vice versa, and

R^e means a hydrogen, C_1-C_6-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkinyl, C_3-C_{10}-cycloalkyl or C_6-C_{12}-aryl, and

p can be a number from 0- 6,

or

R^3 is a radical C = C-R^gR^h, whereby

R^g and R^h, independently of one another, are a hydrogen or a C_1-C_8-alkyl, C_2-C_8-alkenyl or C_2-C_8-alkinyl that optionally is substituted in one or more places, in the same way or differently, with X, in which

X is a cyano, halogen, hydroxy, nitro, $-C(O)R^b$, CO_2R^b, $-O-R^b$, $-C(O)-NR^cR^d$, $-NR^cR^d$ with the meanings, already further mentioned above, for R^b, R^c and R^d, and

R^{4a} and R^{4b}, independently of one another, mean a hydrogen atom, a C_1-C_4-alkyl, a C_2-C_4-alkenyl or together with the ring-carbon atom forming a 3- to 6-membered ring,

A means a monocyclic or bicyclic, carbocyclic or heterocyclic aromatic ring, which optionally can be substituted in one or more places with C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkinyl, C_1-C_6-perfluoroalkyl, C_1-C_6-perfluoroalkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkoxy, $(CH_2)_p$-C_3-C_{10}-cycloalkyl, $(CH_2)_p$-heterocycloalkyl, $(CH_2)_pCN$, $(CH_2)_pHal$, $(CH_2)_pNO_2$, $(CH_2)_p$-C_6-C_{12}-aryl, $(CH_2)_p$-heteroaryl,

$-(CH_2)_pPO_3(R^b)_2$, $-(CH_2)_pNR^cR^d$, $-(CH_2)_pNR^eCOR^b$, $-(CH_2)_pNR^eCSR^b$, $-(CH_2)_pNR^eS(O)R^b$, $-(CH_2)_pNR^eS(O)_2R^b$, $-(CH_2)_pNR^eCONR^cR^d$, $-(CH_2)_pNR^eCOOR^b$, $-(CH_2)_pNR^eC(NH)NR^cR^d$, $-(CH_2)_pNR^eCSNR^cR^d$, $-(CH_2)_pNR^eS(O)NR^cR^d$, $-(CH_2)_pNR^eS(O)_2NR^cR^d$, $-(CH_2)_pCOR^b$, $-(CH_2)_pCSR^b$, $-(CH_2)_p S(O)R^b$, $-(CH_2)_pS(O)(NH)R^b$, $-(CH_2)_pS(O)_2R^b$, $-(CH_2)_pS(O)_2NR^cR^d$, $-(CH_2)_pSO_2OR^b$, $-(CH_2)_pCO_2R^b$, $-(CH_2)_pCONR^cR^d$, $-(CH_2)_pCSNR^cR^d$, $-(CH_2)_pOR^b$, $-(CH_2)_pSR^b$, $-(CH_2)_pCR^b(OH)-R^d$, $-(CH_2)_p-C=NOR^b$, $-O-(CH_2)_n-O-$, $-O-(CH_2)_n-CH_2-$, $-O-CH=CH-$ or $-(CH_2)_{n+2}-$, whereby n = 1 or 2, and the terminal oxygen atoms and/or carbon atoms are linked to directly adjacent ring-carbon atoms, or

A means a radical $-CO_2R^b$, $C(O)NR^cR^d$, COR^b,

or

A means an alkenyl group $-CR^5 = CR^6R^7$, whereby

R^5, R^6 and R^7 are the same or different and, independently of one another, mean hydrogen atoms, halogen atoms, aryl radicals or an unsubstituted or partially or completely fluorinated C_1-C_5–alkyl group, or

A means an alkinyl group $-C\equiv CR^5$, with the meaning cited above for R^5, and

B means a carbonyl group or a CH_2 group

as well as their pharmaceutically acceptable salts.

2. Compounds according to claim 1, in which R^1 and R^2 mean a hydrogen atom, a methyl group or an ethyl group.

3. Compounds according to claim 1, in which R^1 and R^2 together with the C atom of the chain form a ring with a total of 3 to 7 links.

4. Compounds according to claims 1 to 3, in which R^3 means alkenyl, alkinyl, arylalkinyl, heteroarylalkinyl, cycloalkylalkinyl, or heterocycloalkylalkinyl.

5. Compounds according to one of the preceding claims, in which R^3 means a vinyl, ethinyl, propinyl, butinyl, pentinyl, hexinyl, heptinyl, octinyl, hydroxypropinyl, hydroxybutinyl, 3-hydroxy-3-methylbutinyl, hydroxypentinyl, carboxypropinyl, t-butylcarboxypropinyl, phenylethinyl, (hydroxyphenyl)ethinyl, (methoxyphenyl)ethinyl, (dimethylaminophenyl)ethinyl, (methylphenyl)ethinyl, (cyanophenyl)ethinyl, (trifluoromethyl)ethinyl, (diphenyl)ethinyl, (nitrophenyl)ethinyl, (tert-butylphenyl)ethinyl, (acetylphenyl)ethinyl, (acetoxyphenyl)ethinyl, (carboxyphenyl)ethinyl or a benzylethinyl group.

6. Compounds according to one of the preceding claims, in which A is an aromatic ring.

7. Compounds according to one of the preceding claims, in which A is preferably a phenyl or naphthyl radical.

8. Compounds according to claim 7, in which A is an unsubstituted phenyl radical or optionally a phenyl radical that is substituted in one or more places.

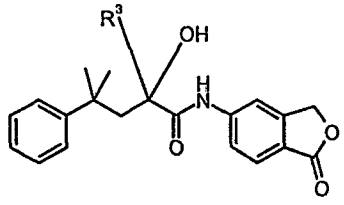
9. Compounds according to claim 8, whereby the phenyl radical is substituted with one or two halogen atoms or a trifluoromethyl group.

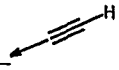
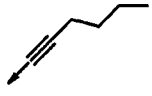
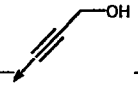
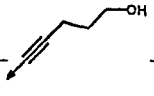
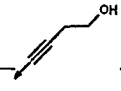
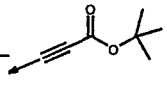
10. Compounds according to claim 9, in which the halogen atoms are chlorine and/or fluorine.

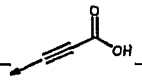
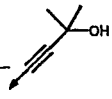
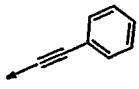
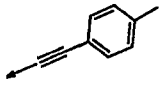
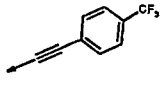
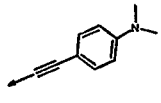
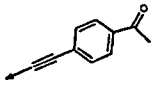
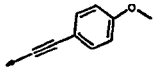
11. Compounds according to claims 1-8, in which A is an $-O-(CH_2)_n-O-$ or $-O-(CH_2)_n-CH_2-$substituted phenyl ring, whereby the respectively directly adjacent ring-carbon atoms are linked.

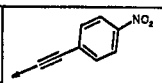
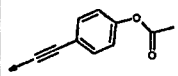
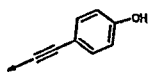
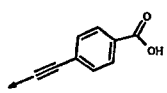
12. Compounds according to one of the preceding claims, in which R^{4a} and R^{4b}, independently of one another, in each case are a hydrogen atom.

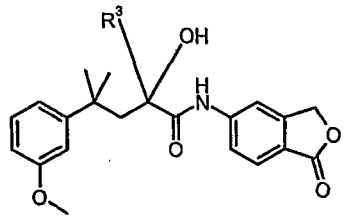
13. Compounds according to claims 1 to 12, namely:

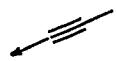
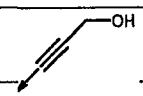
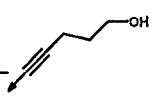
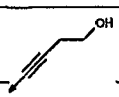
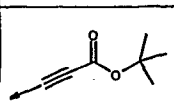


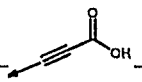
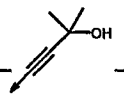
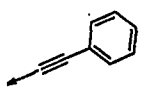
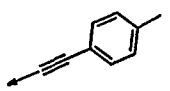
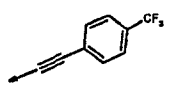
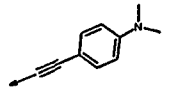
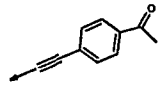
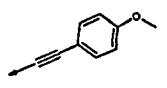
No.	Racemic or Enantiomer	R3
1	rac	
2	+	
3	-	
4	rac	
5	+	
6	-	
7	rac	
8	+	
9	-	
10	rac	
11	+	
12	-	
13	rac	
14	+	
15	-	
16	rac	
17	+	
18	-	
19	rac	
20	+	
21	-	
22	rac	
23	+	

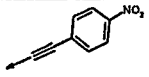
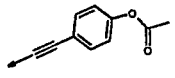
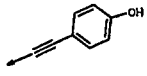
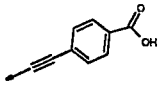
24	-	
25	rac	
26	+	
27	-	
28	rac	
29	+	
30	-	
31	rac	
32	+	
33	-	
34	rac	
35	+	
36	-	
37	rac	
38	+	
39	-	
40	rac	
41	+	
42	-	
43	rac	
44	+	
45	-	
46	rac	
47	+	
48	-	

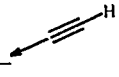
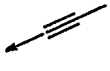
49	rac	
50	+	
51	-	
52	rac	
53	+	
54	-	
55	rac	
56	+	
57	-	
58	rac	
59	+	
60	-	

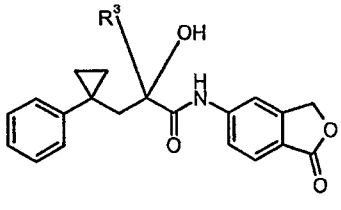


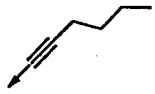
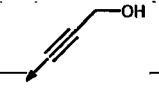
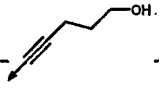
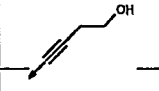
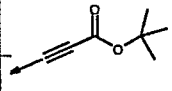
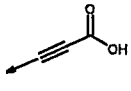
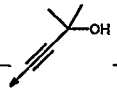
No.	Racemic or Enantiomer	R3
61	rac	
62	+	
63	-	
64	rac	
65	+	
66	-	
67	rac	
68	+	
69	-	
70	rac	
71	+	
72	-	
73	rac	
74	+	
75	-	
76	rac	
77	+	
78	-	
79	rac	
80	+	
81	-	
82	rac	

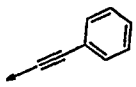
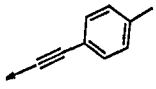
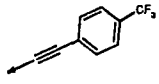
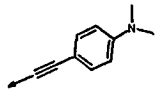
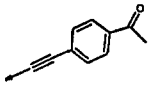
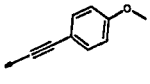
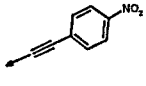
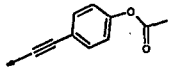
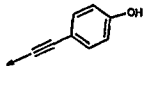
83	+	
84	-	
85	rac	
86	+	
87	-	
88	rac	
89	+	
90	-	
91	rac	
92	+	
93	-	
94	rac	
95	+	
96	-	
97	rac	
98	+	
99	-	
100	rac	
101	+	
102	-	
103	rac	
104	+	
105	-	
106	rac	
107	+	

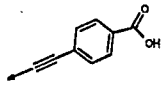
108	-	
109	rac	
110	+	
111	-	
112	rac	
113	+	
114	-	
115	rac	
116	+	
117	-	
118	rac	
119	+	
120	-	

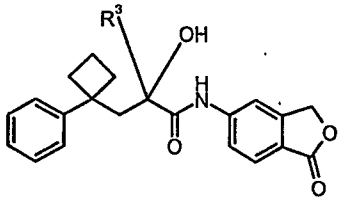
No.	Racemic or Enantiomer	R3
121	rac	
122	+	
123	-	
124	rac	
125	+	
126	-	
127	rac	

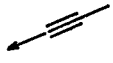
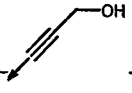


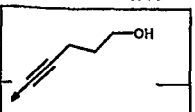
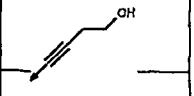
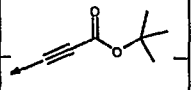
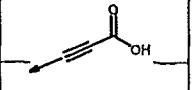
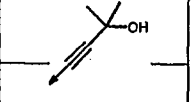
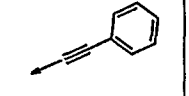
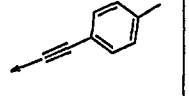
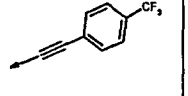
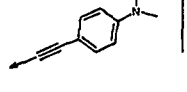
128	+	
129	-	
130	rac	
131	+	
132	-	
133	rac	
134	+	
135	-	
136	rac	
137	+	
138	-	
139	rac	
140	+	
141	-	
142	rac	
143	+	
144	-	
145	rac	
146	+	
147	-	
148	rac	
149	+	
150	-	

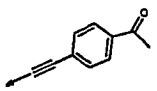
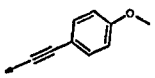
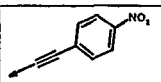
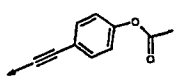
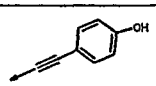
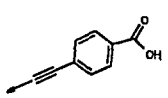
151	rac	
152	+	
153	-	
154	rac	
155	+	
156	-	
157	rac	
158	+	
159	-	
160	rac	
161	+	
162	-	
163	rac	
164	+	
165	-	
166	rac	
167	+	
168	-	
169	rac	
170	+	
171	-	
172	rac	
173	+	
174	-	
175	rac	

176	+	
177	-	
178	rac	
179	+	
180	-	

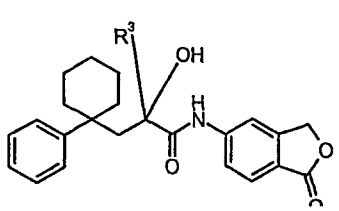


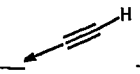
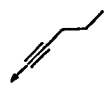
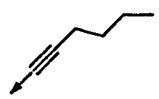
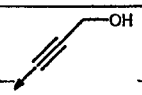
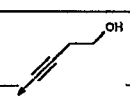
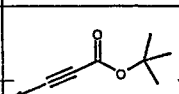
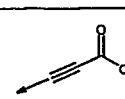
No.	Racemic or Enantiomer	R3
181	rac	
182	+	
183	-	
184	rac	
185	+	
186	-	
187	rac	
188	+	
189	-	
190	rac	
191	+	
192	-	
193	rac	
194	+	
195	-	

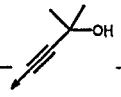
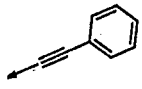
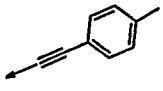
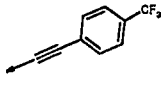
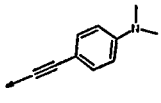
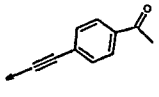
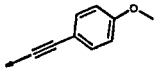
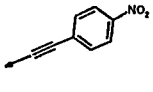
196	rac	
197	+	
198	-	
199	rac	
200	+	
201	-	
202	rac	
203	+	
204	-	
205	rac	
206	+	
207	-	
208	rac	
209	+	
210	-	
211	rac	
212	+	
213	-	
214	rac	
215	+	
216	-	
217	rac	
218	+	
219	-	
220	rac	

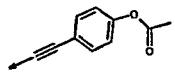
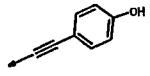
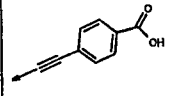
221	+	
222	-	
223	rac	
224	+	
225	-	
226	rac	
227	+	
228	-	
229	rac	
230	+	
231	-	
232	rac	
233	+	
234	-	
235	rac	
236	+	
237	-	
238	rac	
239	+	
240	-	

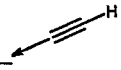
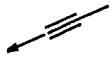
No.	Racemic or Enantiomer	R3

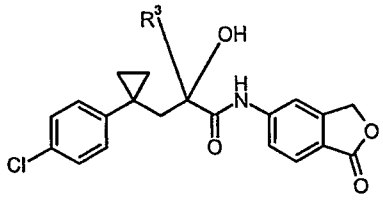


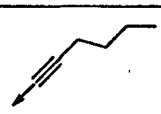
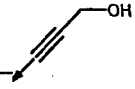
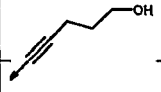
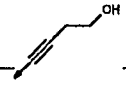
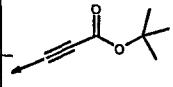
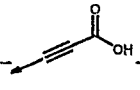
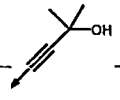
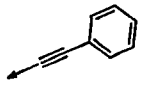
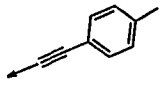
241	rac	
242	+	
243	-	
244	rac	
245	+	
246	-	
247	rac	
248	+	
249	-	
250	rac	
251	+	
252	-	
253	rac	
254	+	
255	-	
256	rac	
257	+	
258	-	
259	rac	
260	+	
261	-	
262	rac	
263	+	
264	-	
265	rac	

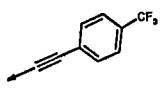
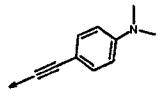
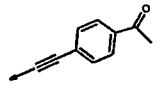
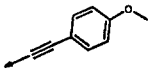
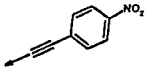
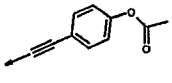
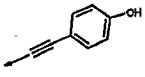
266	+	
267	-	
268	rac	
269	+	
270	-	
271	rac	
272	+	
273	-	
274	rac	
275	+	
276	-	
277	rac	
278	+	
279	-	
280	rac	
281	+	
282	-	
283	rac	
284	+	
285	-	
286	rac	
287	+	
288	-	
289	rac	
290	+	

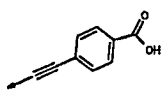
291	-	
292	rac	
293	+	
294	-	
295	rac	
296	+	
297	-	
298	rac	
299	+	
300	-	

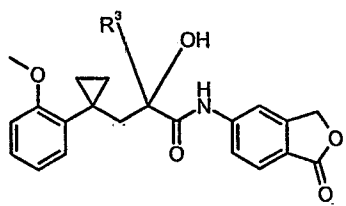
No.	Racemic or Enantiomer	R3
301	rac	
302	+	
303	-	
304	rac	
305	+	
306	-	
307	rac	
308	+	
309	-	

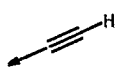
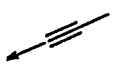
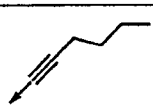
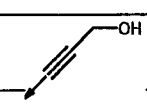
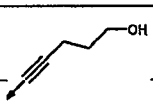


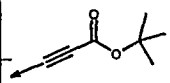
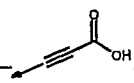
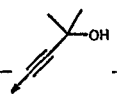
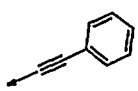
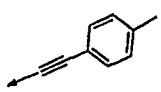
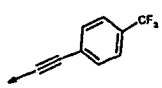
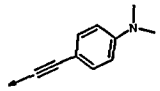
310	rac	
311	+	
312	-	
313	rac	
314	+	
315	-	
316	rac	
317	+	
318	-	
319	rac	
320	+	
321	-	
322	rac	
323	+	
324	-	
325	rac	
326	+	
327	-	
328	rac	
329	+	
330	-	
331	rac	
332	+	
333	-	
334	rac	

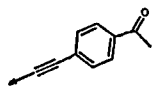
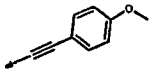
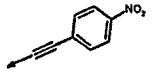
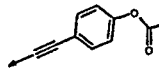
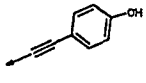
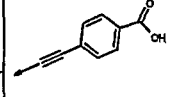
335	+	
336	-	
337	rac	
338	+	
339	-	
340	rac	
341	+	
342	-	
343	rac	
344	+	
345	-	
346	rac	
347	+	
348	-	
349	rac	
350	+	
351	-	
352	rac	
353	+	
354	-	
355	rac	
356	+	
357	-	

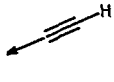
358	rac	
359	+	
360	-	

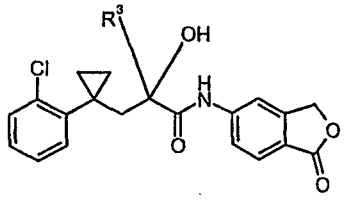


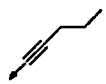
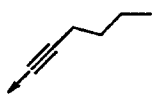
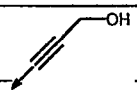
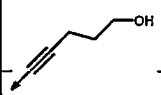
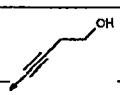
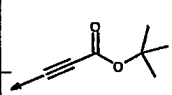
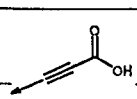
No.	Racemic or Enantiomer	R3
361	rac	
362	+	
363	-	
364	rac	
365	+	
366	-	
367	rac	
368	+	
369	-	
370	rac	
371	+	
372	-	
373	rac	
374	+	
375	-	
376	rac	
377	+	

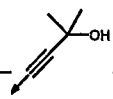
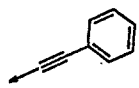
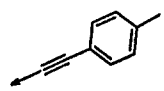
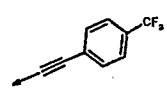
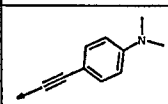
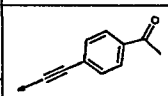
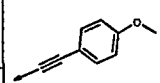
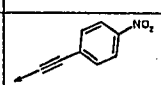
378	-	
379	rac	
380	+	
381	-	
382	rac	
383	+	
384	-	
385	rac	
386	+	
387	-	
388	rac	
389	+	
390	-	
391	rac	
392	+	
393	-	
394	rac	
395	+	
396	-	
397	rac	
398	+	
399	-	
400	rac	

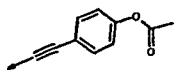
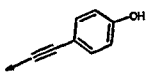
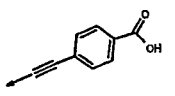
401	+	
402	-	
403	rac	
404	+	
405	-	
406	rac	
407	+	
408	-	
409	rac	
410	+	
411	-	
412	rac	
413	+	
414	-	
415	rac	
416	+	
417	-	
418	rac	
419	+	
420	-	

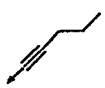
No.	Racemic or Enantiomer	R3
421	rac	

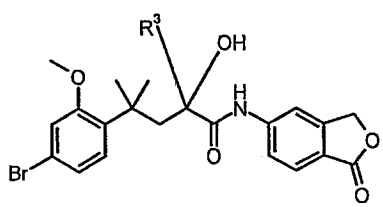


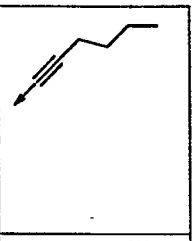
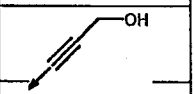
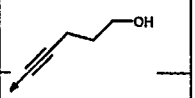
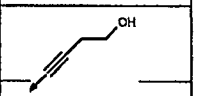
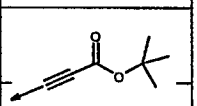
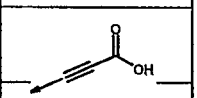
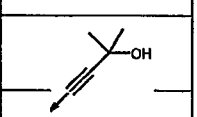
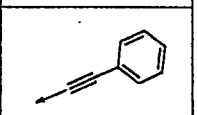
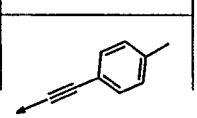
422	+	
423	-	
424	rac	
425	+	
426	-	
427	rac	
428	+	
429	-	
430	rac	
431	+	
432	-	
433	rac	
434	+	
435	-	
436	rac	
437	+	
438	-	
439	rac	
440	+	
441	-	
442	rac	
443	+	
444	-	
445	rac	
446	+	

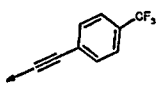
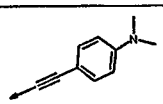
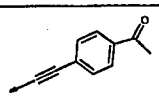
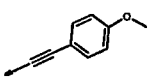
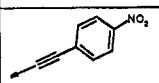
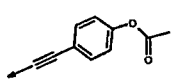
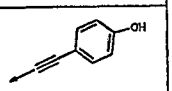
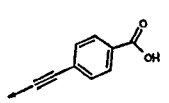
447	-	
448	rac	
449	+	
450	-	
451	rac	
452	+	
453	-	
454	rac	
455	+	
456	-	
457	rac	
458	+	
459	-	
460	rac	
461	+	
462	-	
463	rac	
464	+	
465	-	
466	rac	
467	+	
468	-	
469	rac	
470	+	
471	-	

472	rac	
473	+	
474	-	
475	rac	
476	+	
477	-	
478	rac	
479	+	
480	-	

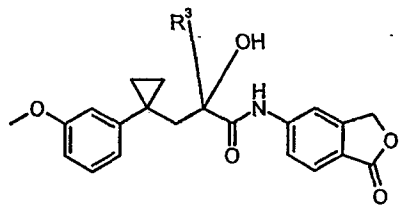
No.	Racemic or Enantiomer	R3
481	rac	
482	+	
483	-	
484	rac	
485	+	
486	-	
487	rac	
488	+	
489	-	

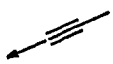
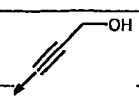
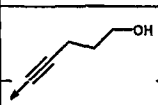
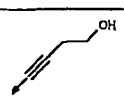


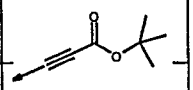
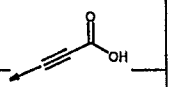
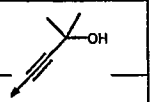
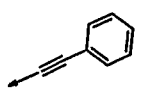
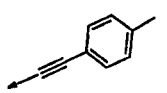
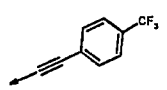
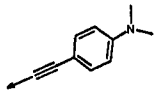
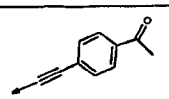
490	rac	
491	+	
492	-	
493	rac	
494	+	
495	-	
496	rac	
497	+	
498	-	
499	rac	
500	+	
501	-	
502	rac	
503	+	
504	-	
505	rac	
506	+	
507	-	
508	rac	
509	+	
510	-	
511	rac	
512	+	
513	-	
214	rac	

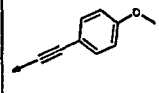
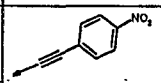
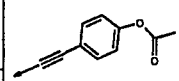
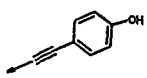
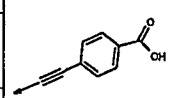
515	+	
516	-	
517	rac	
518	+	
519	-	
520	rac	
521	+	
522	-	
523	rac	
524	+	
525	-	
526	rac	
227	+	
528	-	
529	rac	
530	+	
531	-	
532	rac	
533	+	
534	-	
535	rac	
536	+	
537	-	
538	rac	
539	+	

540	-	

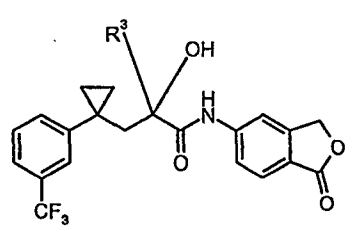


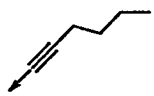
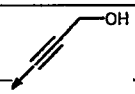
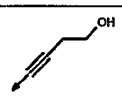
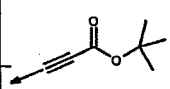
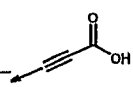
No.	Racemic or Enantiomer	R3
541	rac	
542	+	
543	-	
544	rac	
545	+	
546	-	
547	rac	
548	+	
549	-	
550	rac	
551	+	
552	-	
553	rac	
554	+	
555	-	
556	rac	
557	+	
558	-	
559	rac	

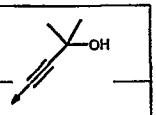
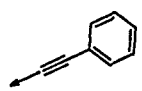
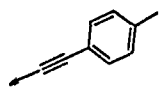
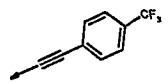
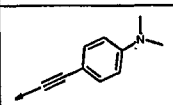
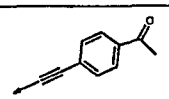
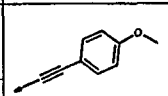
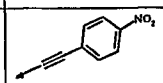
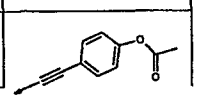
560	+	
561	-	
562	rac	
563	+	
564	-	
565	rac	
566	+	
567	-	
568	rac	
569	+	
570	-	
571	rac	
572	+	
573	-	
574	rac	
575	+	
576	-	
577	rac	
578	+	
579	-	
580	rac	
581	+	
582	-	
583	rac	
584	+	

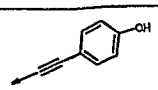
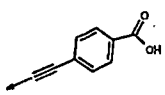
585	-	
586	rac	
587	+	
588	-	
589	rac	
590	+	
591	-	
592	rac	
593	+	
594	-	
595	rac	
596	+	
597	-	
598	rac	
599	+	
600	-	

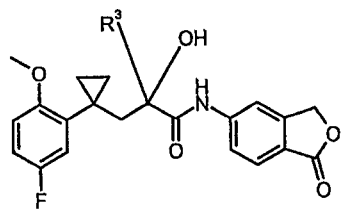
No.	Racemic or Enantiomer	R3
601	rac	
602	+	
603	-	
604	rac	

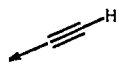
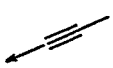
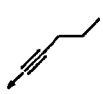


605	+	
606	-	
607	rac	
608	+	
609	-	
610	rac	
611	+	
612	-	
613	rac	
614	+	
615	-	
616	rac	
617	+	
618	-	
619	rac	
620	+	
621	-	
622	rac	
623	+	
624	-	
625	rac	
626	+	
627	-	

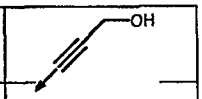
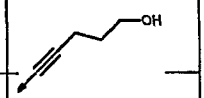
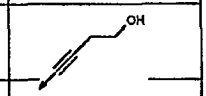
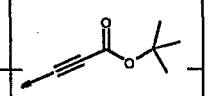
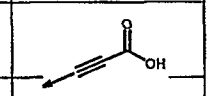
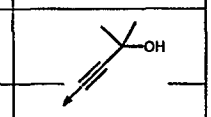
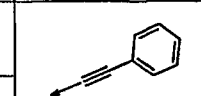
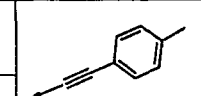
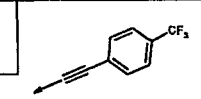
628	rac	
629	+	
630	-	
631	rac	
632	+	
633	-	
634	rac	
635	+	
636	-	
637	rac	
638	+	
639	-	
640	rac	
641	+	
642	-	
643	rac	
644	+	
645	-	
646	rac	
647	+	
648	-	
649	rac	
650	+	
651	-	
652	rac	

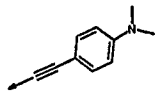
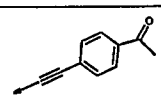
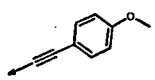
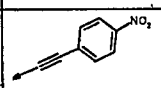
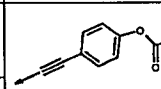
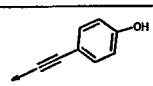
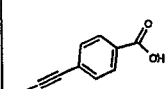
653	+	
654	-	
655	rac	
656	+	
657	-	
658	rac	
659	+	
660	-	

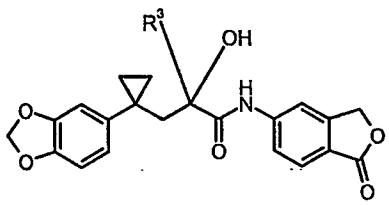


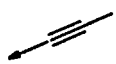
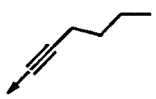
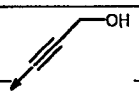
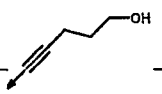
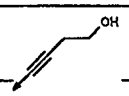
No.	Racemic or Enantiomer	R3
661	rac	
662	+	
663	-	
664	rac	
665	+	
666	-	
667	rac	
668	+	
669	-	
670	rac	
671	+	
672	-	

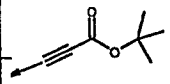
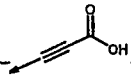
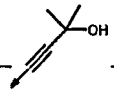
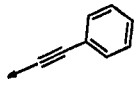
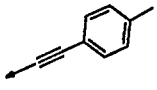
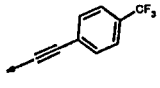
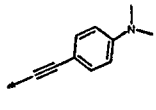
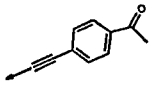
200

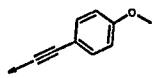
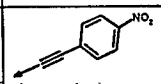
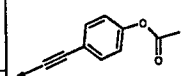
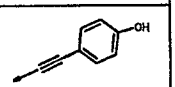
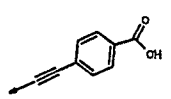
673	rac	
674	+	
675	-	
676	rac	
677	+	
678	-	
679	rac	
680	+	
681	-	
682	rac	
683	+	
684	-	
685	rac	
686	+	
687	-	
688	rac	
689	+	
690	-	
691	rac	
692	+	
693	-	
694	rac	
695	+	
696	-	
697	rac	

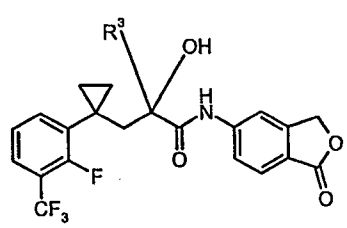
698	+	
699	-	
700	rac	
701	+	
702	-	
703	rac	
704	+	
705	-	
706	rac	
707	+	
708	-	
709	rac	
710	+	
711	-	
712	rac	
713	+	
714	-	
715	rac	
716	+	
717	-	
718	rac	
719	+	
720	-	

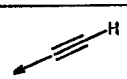
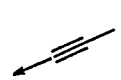


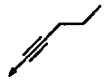
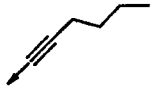
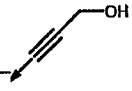
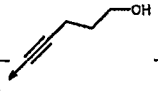
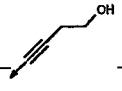
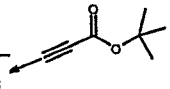
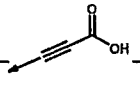
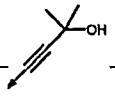
No.	Racemic or Enantiomer	R3
721	rac	
722	+	
723	-	
724	rac	
725	+	
726	-	
727	rac	
728	+	
729	-	
730	rac	
731	+	
732	-	
733	rac	
734	+	
735	-	
736	rac	
737	+	
738	-	
739	rac	
740	+	
741	-	

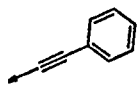
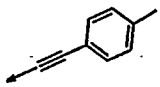
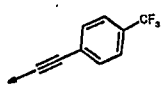
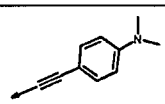
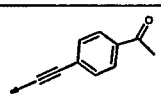
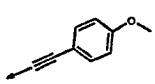
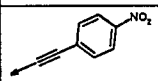
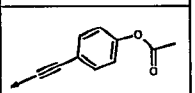
742	rac	
743	+	
744	-	
745	rac	
746	+	
747	-	
748	rac	
749	+	
750	-	
751	rac	
752	+	
753	-	
754	rac	
755	+	
756	-	
757	rac	
758	+	
759	-	
760	rac	
761	+	
762	-	
763	rac	
764	+	

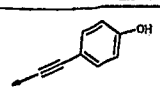
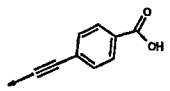
765	-	
766	rac	
767	+	
768	-	
769	rac	
770	+	
771	-	
772	rac	
773	+	
774	-	
775	rac	
776	+	
777	-	
778	rac	
779	+	
780	-	

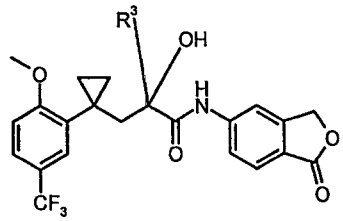


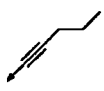
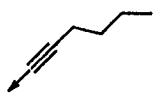
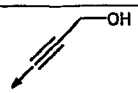
No.	Racemic or Enantiomer	R3
781	rac	
782	+	
783	-	
784	rac	

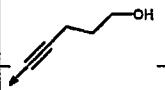
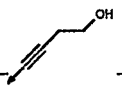
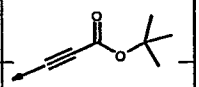
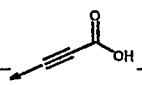
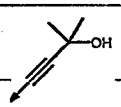
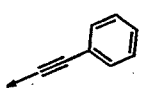
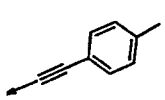
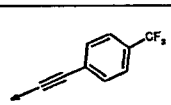
785	+	
786	-	
787	rac	
788	+	
789	-	
790	rac	
791	+	
792	-	
793	rac	
794	+	
795	-	
796	rac	
797	+	
798	-	
799	rac	
800	+	
801	-	
802	rac	
803	+	
804	-	
805	rac	
806	+	
807	-	
808	rac	
809	+	

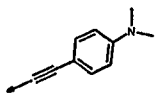
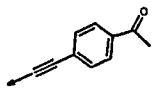
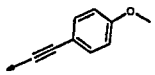
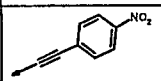
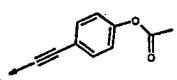
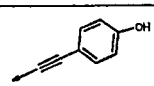
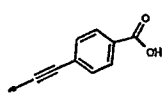
810	-	
811	rac	
812	+	
813	-	
814	rac	
815	+	
816	-	
817	rac	
818	+	
819	-	
820	rac	
821	+	
822	-	
823	rac	
824	+	
825	-	
826	rac	
827	+	
828	-	
829	rac	
830	+	
831	-	
832	rac	
833	+	
834	-	

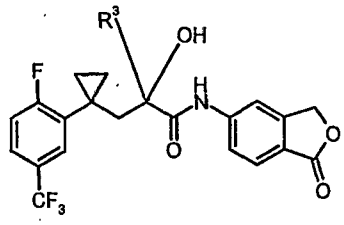
835	rac	
836	+	
837	-	
838	rac	
839	+	
840	-	

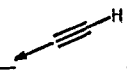
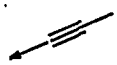
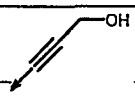
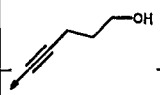
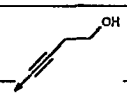
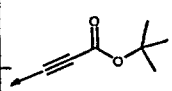


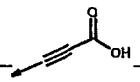
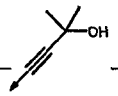
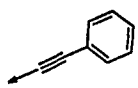
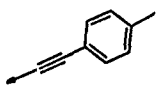
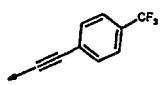
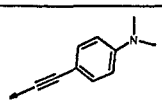
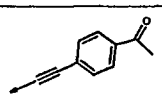
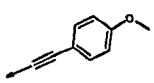
No.	Racemic or Enantiomer	R3
841	rac	
842	+	
843	-	
844	rac	
845	+	
846	-	
847	rac	
848	+	
849	-	
850	rac	
851	+	
852	-	
853	rac	

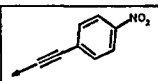
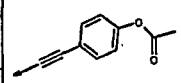
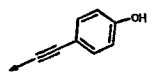
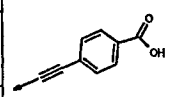
854	+	
855	-	
856	rac	
857	+	
858	-	
859	rac	
860	+	
861	-	
862	rac	
863	+	
864	-	
865	rac	
866	+	
867	-	
868	rac	
869	+	
870	-	
871	rac	
872	+	
873	-	
874	rac	
875	+	
876	-	
877	rac	
878	+	

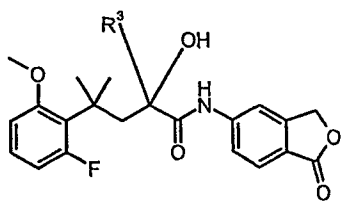
879	-	
880	rac	
881	+	
882	-	
883	rac	
884	+	
885	-	
886	rac	
887	+	
888	-	
889	rac	
890	+	
891	-	
892	rac	
893	+	
894	-	
895	rac	
896	+	
897	-	
898	rac	
899	+	
900	-	

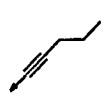


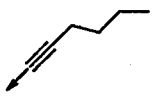
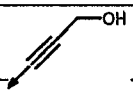
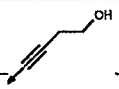
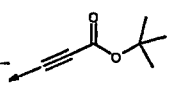
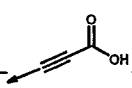
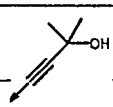
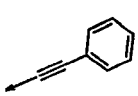
No.	Racemic or Enantiomer	R3
901	rac	
902	+	
903	-	
904	rac	
905	+	
906	-	
907	rac	
908	+	
909	-	
910	rac	
911	+	
912	-	
913	rac	
914	+	
915	-	
916	rac	
917	+	
918	-	
919	rac	
920	+	
921	-	
922	rac	
923	+	

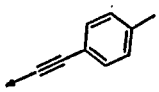
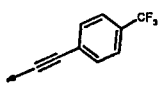
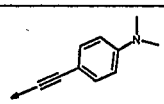
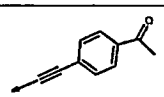
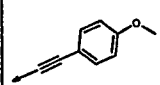
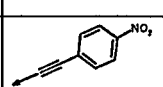
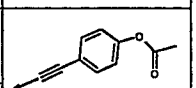
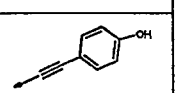
924	-	
925	rac	
926	+	
927	-	
928	rac	
929	+	
930	-	
931	rac	
932	+	
933	-	
934	rac	
935	+	
936	-	
937	rac	
938	+	
939	-	
940	rac	
941	+	
942	-	
943	rac	
944	+	
945	-	
946	rac	
947	+	
948	-	

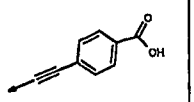
949	rac	
950	+	
951	-	
952	rac	
953	+	
954	-	
955	rac	
956	+	
957	-	
958	rac	
959	+	
960	-	

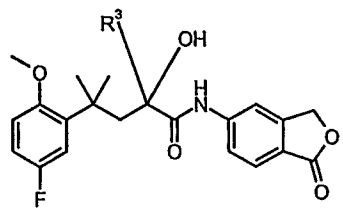


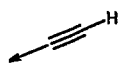
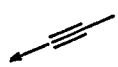
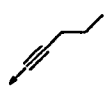
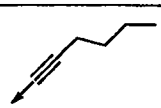
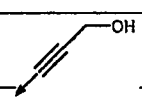
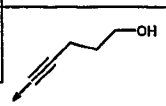
No.	Racemic or Enantiomer	R3
961	rac	
962	+	
963	-	
964	rac	
965	+	
966	-	
967	rac	
968	+	

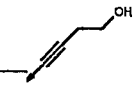
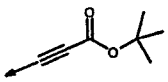
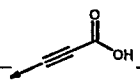
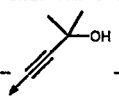
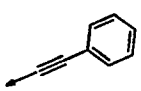
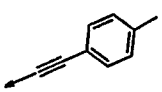
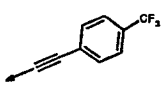
969	-	
970	rac	
971	+	
972	-	
973	rac	
974	+	
975	-	
976	rac	
977	+	
978	-	
979	rac	
980	+	
981	-	
982	rac	
983	+	
984	-	
985	rac	
986	+	
987	-	
988	rac	
989	+	
990	-	
991	rac	
992	+	
993	-	

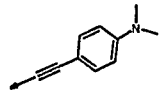
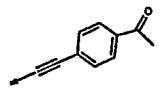
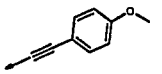
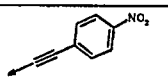
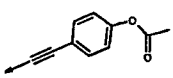
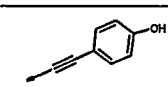
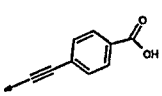
994	rac	
995	+	
996	-	
997	rac	
998	+	
999	-	
1000	rac	
1001	+	
1002	-	
1003	rac	
1004	+	
1005	-	
1006	rac	
1007	+	
1008	-	
1009	rac	
1010	+	
1011	-	
1012	rac	
1013	+	
1014	-	
1015	rac	
1016	+	

1017	-	
1018	rac	
1019	+	
1020	-	

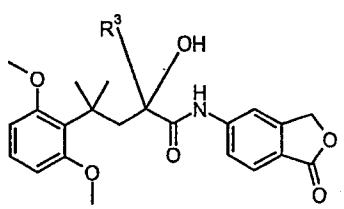


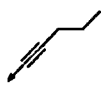
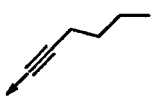
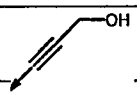
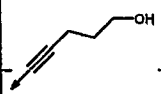
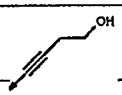
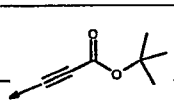
No.	Racemic or Enantiomer	R3
1021	rac	
1022	+	
1023	-	
1024	rac	
1025	+	
1026	-	
1027	rac	
1028	+	
1029	-	
1030	rac	
1031	+	
1032	-	
1033	rac	
1034	+	
1035	-	
1036	rac	

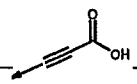
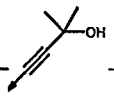
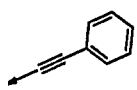
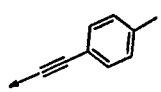
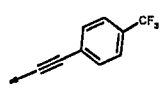
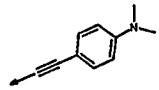
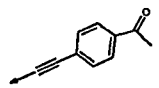
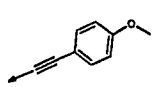
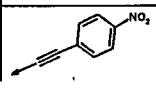
1037	+	
1038	-	
1039	rac	
1040	+	
1041	-	
1042	rac	
1043	+	
1044	-	
1045	rac	
1046	+	
1047	-	
1048	rac	
1049	+	
1050	-	
1051	rac	
1052	+	
1053	-	
1054	rac	
1055	+	
1056	-	
1057	rac	
1058	+	
1059	-	

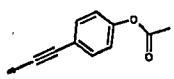
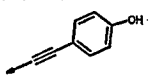
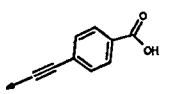
1060	rac	
1061	+	
1062	-	
1063	rac	
1064	+	
1065	-	
1066	rac	
1067	+	
1068	-	
1069	rac	
1070	+	
1071	-	
1072	rac	
1073	+	
1074	-	
1075	rac	
1076	+	
1077	-	
1078	rac	
1079	+	
1080	-	

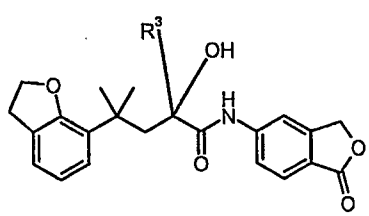
No.	Racemic or	R3

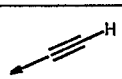
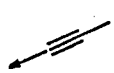
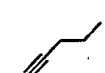


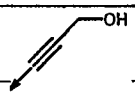
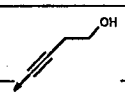
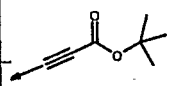
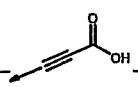
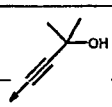
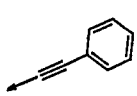
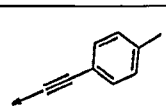
	Enantiomer	
1081	rac	
1082	+	
1083	-	
1084	rac	
1085	+	
1086	-	
1087	rac	
1088	+	
1089	-	
1090	rac	
1091	+	
1092	-	
1093	rac	
1094	+	
1095	-	
1096	rac	
1097	+	
1098	-	
1099	rac	
1100	+	
1101	-	
1102	rac	
1103	+	
1104	-	

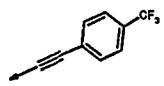
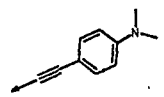
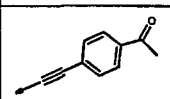
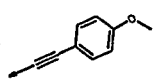
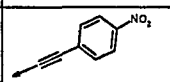
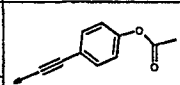
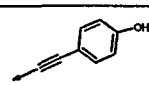
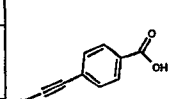
1105	rac	
1106	+	
1107	-	
1108	rac	
1109	+	
1110	-	
1111	rac	
1112	+	
1113	-	
1114	rac	
1115	+	
1116	-	
1117	rac	
1118	+	
1119	-	
1120	rac	
1121	+	
1122	-	
1123	rac	
1124	+	
1125	-	
1126	rac	
1127	+	
1128	-	
1129	rac	

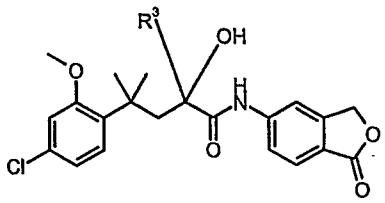
1130	+	
1131	-	
1132	rac	
1133	+	
1134	-	
1135	rac	
1136	+	
1137	-	
1138	rac	
1139	+	
1140	-	

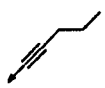
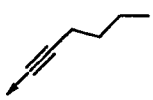
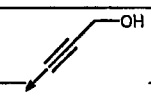
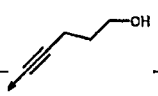
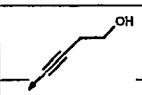


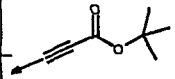
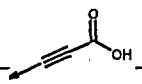
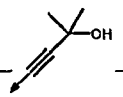
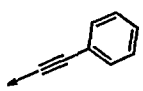
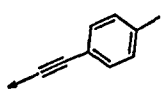
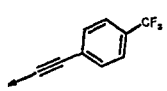
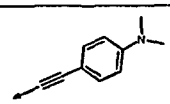
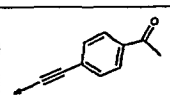
No.	Racemic or Enantiomer	R3
1141	rac	
1142	+	
1143	-	
1144	rac	
1145	+	
1146	-	
1147	rac	
1148	+	
1149	-	
1150	rac	

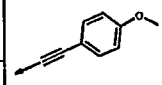
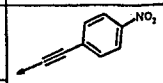
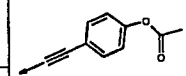
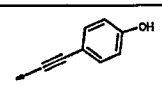
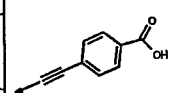
1151	+	
1152	-	
1153	rac	
1154	+	
1155	-	
1156	rac	
1157	+	
1158	-	
1159	rac	
1160	+	
1161	-	
1162	rac	
1163	+	
1164	-	
1165	rac	
1166	+	
1167	-	
1168	rac	
1169	+	
1170	-	
1171	rac	
1172	+	
1173	-	
1174	rac	
1175	+	

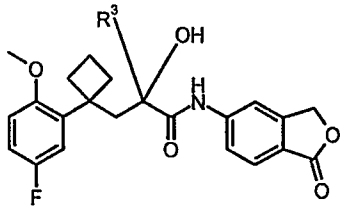
1176	-	
1177	rac	
1178	+	
1179	-	
1180	rac	
1181	+	
1182	-	
1183	rac	
1184	+	
1185	-	
1186	rac	
1187	+	
1188	-	
1189	rac	
1190	+	
1191	-	
1192	rac	
1193	+	
1194	-	
1195	rac	
1196	+	
1197	-	
1198	rac	
1199	+	
1200	-	

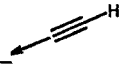
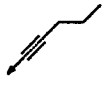
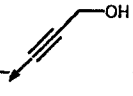
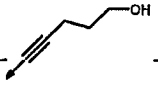
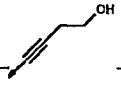


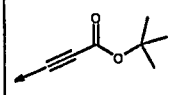
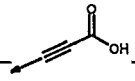
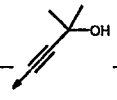
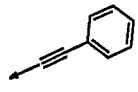
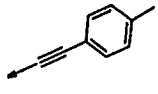
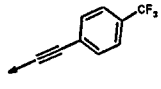
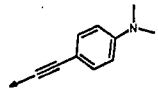
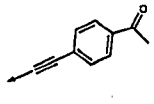
No.	Racemic or Enantiomer	R3
1201	rac	
1202	+	
1203	-	
1204	rac	
1205	+	
1206	-	
1207	rac	
1208	+	
1209	-	
1210	rac	
1211	+	
1212	-	
1213	rac	
1214	+	
1215	-	
1216	rac	
1217	+	
1218	-	
1219	rac	
1220	+	
1221	-	

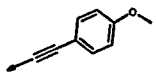
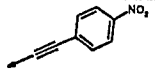
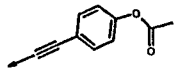
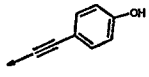
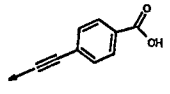
1222	rac	
1223	+	
1224	-	
1225	rac	
1226	+	
1227	-	
1228	rac	
1229	+	
1230	-	
1231	rac	
1232	+	
1233	-	
1234	rac	
1235	+	
1236	-	
1237	rac	
1238	+	
1239	-	
1240	rac	
1241	+	
1242	-	
1243	rac	
1244	+	

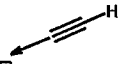
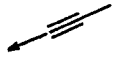
1245	-	
1246	rac	
1247	+	
1248	-	
1249	rac	
1250	+	
1251	-	
1252	rac	
1253	+	
1254	-	
1255	rac	
1256	+	
1257	-	
1258	rac	
1259	+	
1260	-	

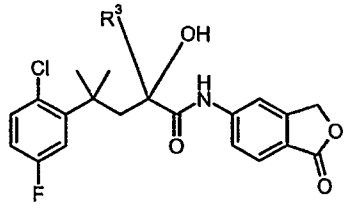


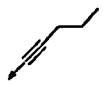
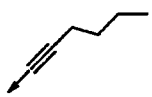
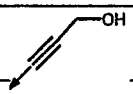
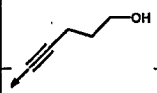
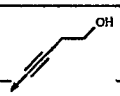
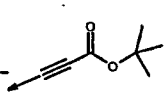
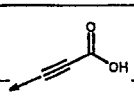
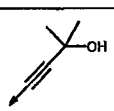
No.	Racemic or Enantiomer	R3
1261	rac	
1262	+	
1263	-	
1264	rac	
1265	+	
1266	-	
1267	rac	
1268	+	
1269	-	
1270	rac	
1271	+	
1272	-	
1273	rac	
1274	+	
1275	-	
1276	rac	
1277	+	
1278	-	
1279	rac	
1280	+	
1281	-	

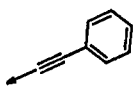
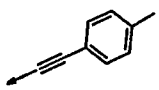
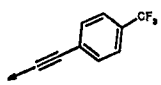
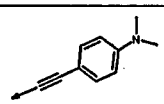
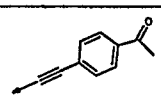
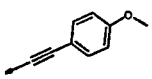
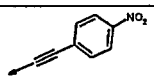
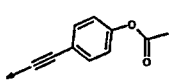
1282	rac	
1283	+	
1284	-	
1285	rac	
1286	+	
1287	-	
1288	rac	
1289	+	
1290	-	
1291	rac	
1292	+	
1293	-	
1294	rac	
1295	+	
1296	-	
1297	rac	
1298	+	
1299	-	
1300	rac	
1301	+	
1302	-	
1303	rac	
1304	+	
1305	-	

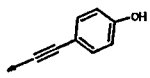
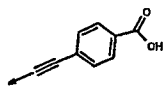
1306	rac	
1307	+	
1308	-	
1309	rac	
1310	+	
1311	-	
1312	rac	
1313	+	
1314	-	
1315	rac	
1316	+	
1317	-	
1318	rac	
1319	+	
1320	-	

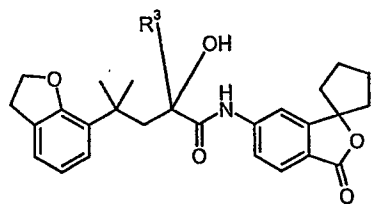
No.	Racemic or Enantiomer	R3
1321	rac	
1322	+	
1323	-	
1324	rac	
1325	+	

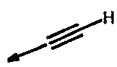
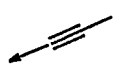
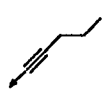
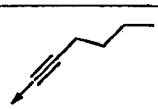


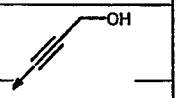
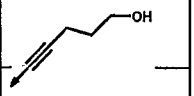
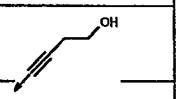
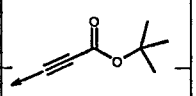
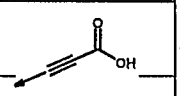
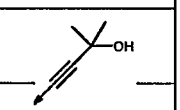
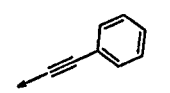
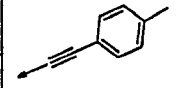
1326	-	
1327	rac	
1328	+	
1329	-	
1330	rac	
1331	+	
1332	-	
1333	rac	
1334	+	
1335	-	
1336	rac	
1337	+	
1338	-	
1339	rac	
1340	+	
1341	-	
1342	rac	
1343	+	
1344	-	
1345	rac	
1346	+	
1347	-	
1348	rac	

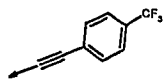
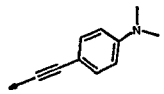
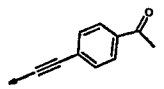
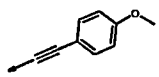
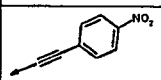
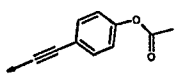
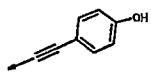
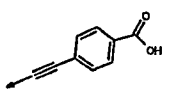
1349	+	
1350	-	
1351	rac	
1352	+	
1353	-	
1354	rac	
1355	+	
1356	-	
1357	rac	
1358	+	
1359	-	
1360	rac	
1361	+	
1362	-	
1363	rac	
1364	+	
1365	-	
1366	rac	
1367	+	
1368	-	
1369	rac	
1370	+	
1371	-	
1372	rac	
1373	+	

1374	-	
1375	rac	
1376	+	
1377	-	
1378	rac	
1379	+	
1380	-	

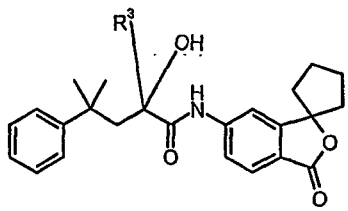


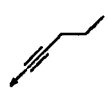
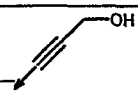
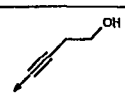
No.	Racemic or Enantiomer	R3
1381	rac	
1382	+	
1383	-	
1384	rac	
1385	+	
1386	-	
1387	rac	
1388	+	
1389	-	
1390	rac	
1391	+	

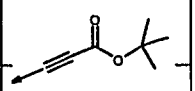
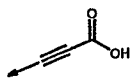
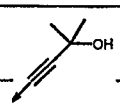
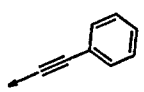
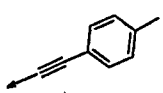
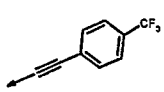
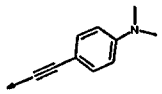
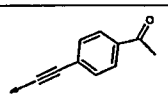
1392	-	
1393	rac	
1394	+	
1395	-	
1396	rac	
1397	+	
1398	-	
1399	rac	
1400	+	
1401	-	
1402	rac	
1403	+	
1404	-	
1405	rac	
1406	+	
1407	-	
1408	rac	
1409	+	
1410	-	
1411	rac	
1412	+	
1413	-	
1414	rac	
1415	+	
1416	-	

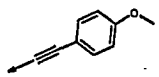
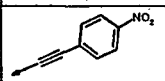
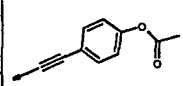
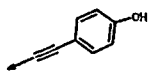
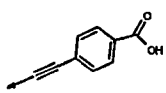
1417	rac	
1418	+	
1419	-	
1420	rac	
1421	+	
1422	-	
1423	rac	
1424	+	
1425	-	
1426	rac	
1427	+	
1428	-	
1429	rac	
1430	+	
1431	-	
1432	rac	
433	+	
1434	-	
1435	rac	
1436	+	
1437	-	
1438	rac	
1439	+	

1440	-	

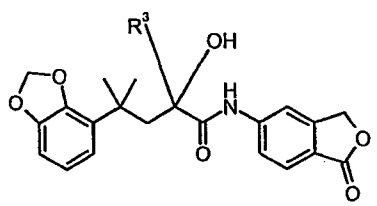


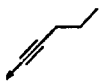
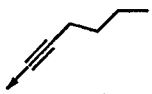
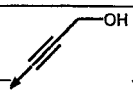
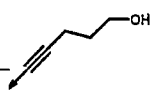
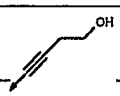
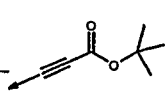
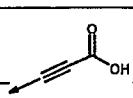
No.	Racemic or Enantiomer	R3
1441	rac	
1442	+	
1443	-	
1444	rac	
1445	+	
1446	-	
1447	rac	
1448	+	
1449	-	
1450	rac	
1451	+	
1452	-	
1453	rac	
1454	+	
1455	-	
1456	rac	
1457	+	
1458	-	
1459	rac	

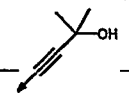
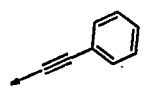
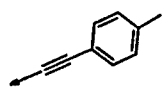
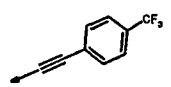
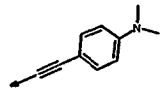
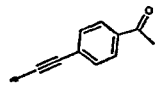
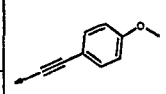
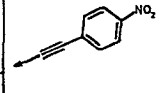
1460	+	
1461	-	
1462	rac	
1463	+	
1464	-	
1465	rac	
1466	+	
1467	-	
1468	rac	
1469	+	
1470	-	
1471	rac	
1472	+	
1473	-	
1474	rac	
1475	+	
1476	-	
1477	rac	
1478	+	
1479	-	
1480	rac	
1481	+	
1482	-	
1483	rac	

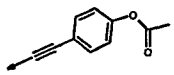
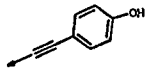
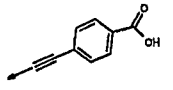
1484	+	
1485	-	
1486	rac	
1487	+	
1488	-	
1489	rac	
1490	+	
1491	-	
1492	rac	
1493	+	
1494	-	
1495	rac	
1496	+	
1497	-	
1498	rac	
1499	+	
1500	-	

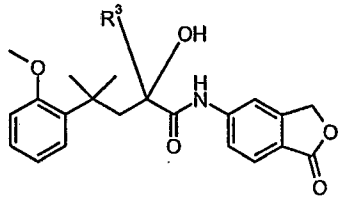
No.	Racemic or Enantiomer	R3
1501	rac	
1502	+	
1503	-	

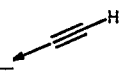
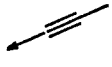
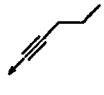


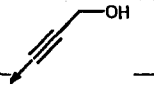
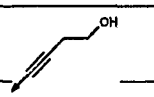
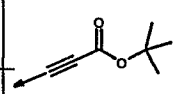
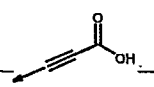
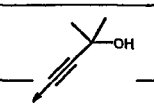
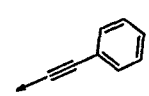
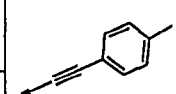
1504	rac	
1505	+	
1506	-	
1507	rac	
1508	+	
1509	-	
1510	rac	
1511	+	
1512	-	
1513	rac	
1514	+	
1515	-	
1516	rac	
1517	+	
1518	-	
1519	rac	
1520	+	
1521	-	
1522	rac	
1523	+	
1524	-	
1525	rac	
1526	+	

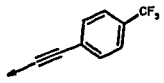
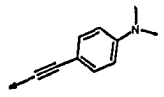
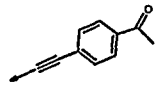
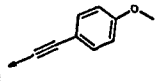
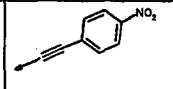
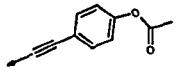
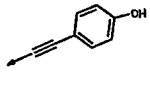
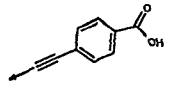
1527	-	
1528	rac	
1529	+	
1530	-	
1531	rac	
1532	+	
1533	-	
1534	rac	
1535	+	
1536	-	
1537	rac	
1538	+	
1539	-	
1540	rac	
1541	+	
1542	-	
1543	rac	
1544	+	
1545	-	
1546	rac	
1547	+	
1548	-	
1549	rac	
1550	+	
1551	-	

1552	rac	
1553	+	
1554	-	
1555	rac	
1556	+	
1557	-	
1558	rac	
1559	+	
1560	-	



No.	Racemic or Enantiomer	R3
1561	rac	
1562	+	
1563	-	
1564	rac	
1565	+	
1566	-	
1567	rac	
1568	+	
1569	-	
1570	rac	
1571	+	

1572	-	
1573	rac	
1574	+	
1575	-	
1576	rac	
1577	+	
1578	-	
1579	rac	
1580	+	
1581	-	
1582	rac	
1583	+	
1584	-	
1585	rac	
1586	+	
1587	-	
1588	rac	
1589	+	
1590	-	
1591	rac	
1592	+	
1593	-	
1594	rac	
1595	+	
1596	-	

1597	rac	
1598	+	
1599	-	
1600	rac	
1601	+	
1602	-	
1603	rac	
1604	+	
1605	-	
1606	rac	
1607	+	
1608	-	
1609	rac	
1610	+	
1611	-	
1612	rac	
1613	+	
1614	-	
1615	rac	
1616	+	
1617	-	
1618	rac	
1619	+	

1620	-	

14. Pharmaceutical composition that contains at least one compound of general formula I according to one of claims 1 to 13 and optionally at least one additional active ingredient together with pharmaceutically compatible adjuvants and/or vehicles.

15. Pharmaceutical composition according to claim 14, wherein the additional active ingredient is a SERM (selective estrogen receptor modulator), an aromatase inhibitor, an antiestrogen, or a prostaglandin.

16. Pharmaceutical composition according to claim 14, whereby the active ingredients can be tamoxifen, 5-(4-{5-[(RS)-(4,4,5,5,5-pentafluoropentyl)sulfinyl]-pentyloxy}phenyl)-6-phenyl-8,9-dihydro-7H-benzocyclohepten-2-ol, ICI 182 780 (7alpha-[9-(4,4,5,5-pentafluoropentylsulfinyl)nonyl]estra-1,3,5(10)-triene-3,17-beta-diol), 11beta-fluoro-7alpha-[5-(methyl{3-[(4,4,5,5,5-pentafluoropentyl)sulfanyl]propyl}amino)pentyl]estra-1,3,5(10)-triene-3,17beta-diol, 11beta-fluoro-7alpha-{5-[methyl(7,7,8,8,9,9,10,10,10-nonafluorodecyl)amino]pentyl}estra-1,3,5(10)-triene-3,17beta-diol, 11beta-fluoro-17alpha-methyl-7alpha-{5-[methyl(8,8,9,9,9-pentafluorononyl)amino]pentyl}estra-1,3,5(10)-triene-3,17beta-diol, clomifene, raloxifene, fadrozole, formestane, letrozole, anastrozole or atamestane.

17. Compounds according to one of claims 1 to 13 for the manufacture of a medicament.

18. Use of compounds according to claim 1-13 for the manufacture of a medicament for therapy and prophylaxis of gynecological diseases such as endometriosis, leiomyomas of the uterus, dysfunctional bleeding and dysmenorrhea.

19. Use of compounds according to claim 1-13 for the production of a pharmaceutical agent for therapy and prophylaxis of hormone-dependent tumors.

20. Use of compounds according to claim 1-13 for the production of a pharmaceutical agent for therapy and prophylaxis of breast cancer.

21. Use of compounds according to claim 1-13 for the production of a pharmaceutical agent for therapy and prophylaxis of endometrial carcinoma.

22. Use of compounds according to claim 1-13 for the production of a pharmaceutical agent for therapy and prophylaxis of ovarian cancer.

23. Use of compounds according to claim 1-13 for the production of a pharmaceutical agent for therapy and prophylaxis of prostate cancer.

24. Use of compounds according to claim 1-13 for the production of a pharmaceutical agent for female hormone replacement therapy.

25. Use of compounds according to claim 1-13 for female birth control.

(12) **Publicación de la solicitud internacional bajo PCT**
(19) **Organización Mundial de Propiedad Intelectual**
Oficina Internacional
(43) **Fecha de publicación internacional : 28 de diciembre de 2006 (28.12.2006)**
(10) **Número de publicación internacional: WO 2006/136462 A1**

(51) **Clasificación internacional de patentes:**
C07D 307/83 (2006.01) **A61K 31/335** (2006.01)
C07D 307/94 (2006.01) **A61P 15/00** (2006.01)
C07D 407/12 (2006.01) **A61P 35/00** (2006.01)
(21) **Número de solicitud internacional**: PCT/EP2006/006532
(22) **Fecha de presentación internacional**: 22 de junio de 2006 (22.06.2006)
(25) **Idioma de la presentación**: inglés
(26) **Idioma de la publicación**: inglés
(30) **Antecedentes de prioridad**:
10 2005 030 294.7 del 24 de junio de 2005 (24.06.2005) DE
(71) **Solicitante (para todos los estados designados con excepción de US): SCHERING AKTIENGESELLSCHAFT** [DE/DE]; Müllerstrasse 178, 13353 Berlin (DE).
(72) **Inventores; y**
(75) **Inventor/Solicitante** *(solamente para US):* **SCHWEDE, Wolfgang** [DE/DE]; Magdeburger Strasse 41a, 16548 Glienicke (DE). **MOELLER, Carsten** [DE/DE]; Windscheidstrasse 22, 10627 Berlin (DE). **SCHMIDT, Anja** [DE/DE]; Wielandstrasse 11, 10529 Berlin (DE). **FUHRMANN, Ulrike** [DE/DE]; Charlottenburger Ufer 4, 10587 Berlin (DE). **SCHMEES, Norbert** [DE/DE]; Bondickstrasse 61, 13469 Berlin (DE). **BOTHE, Ulrich** [DE/DE]; Bredowstrasse 24, 10551 Berlin (DE).
(81) **Estados designados** (en la medida en que no se indique lo contrario, para cada tipo de protección nacional disponible): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.
(84) **Estados designados** (en la medida en que no se indique lo contrario, para cada tipo de protección regional disponible): Patente ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Patente euroasiatica (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Patente europea (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), Patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

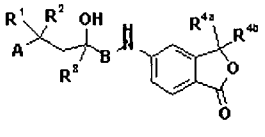
Publicado:
- con el informe de búsqueda internacional
- con reivindicaciones enmendadas y una declaración

Véanse las explicaciones („Guidance Notes on Codes an Abbreviations") al comienzo de cada edicion regular de la Gaceta-PCT para la explicación del código de dos dígitos y de las otras abreviaturas

---

(54) Título: DERIVADOS DE BENZOFURARONA COMO MODULADORES NO ESTEROIDES DE RECEPTORES DE PROGESTERONA

(57) Resumen



(I)

La presente invención se refiere a moduladores no esteroides del receptor de progesterona de la fórmula general I, al proceso para su producción, al uso de los moduladores del receptor de progesterona para la preparación de agentes farmacéuticos así como también composiciones farmacéuticas que contienen estos compuestos. Los compuestos según la invención son apropiados para la terapia y la prevención de enfermedades ginecológicas tales como endometriosis, leiomiomas de útero, hemorragias disfuncionales y dismenorrea y para la terapia y la prevención de tumores dependientes de hormonas y para el uso para el control de la fertilidad femenina y para la terapia de reemplazo hormonal.

DERIVADOS DE BENZOFURARONA COMO MODULADORES NO ESTEROIDES DE RECEPTORES DE PROGESTERONA

MEMORIA DESCRIPTIVA

La presente invención se refiere a moduladores no esteroides de receptores de progesterona, un proceso para producirlos, el uso de moduladores de receptores de progesterona para la preparación de agentes farmacéuticos y composiciones farmacéuticas que contienen estos compuestos.

La hormona esteroide progesterona regula de manera decisiva el proceso de reproducción en el organismo femenino. La progesterona se segrega durante el ciclo y el embarazo en grandes cantidades del ovario o la placenta. Al interactuar con los estrógenos, la progesterona ocasiona alteraciones cíclicas de la membrana mucosa del útero (endometrio) en el ciclo menstrual. Bajo la influencia de mayores niveles de progesterona después de la ovulación, el endometrio pasa a un estado que permite que anide un embrión (blastocistos). En el embarazo, la progesterona controla la relajación del miometrio y conserva la función del tejido de la decidua.

Se sabe además que la progesterona inhibe la proliferación del endometrio por supresión de la mitosis mediada por estrógenos en el tejido uterino (K. Chwalisz, R. M. Brenner,

U. Fuhrmann, H. Hess-Stumpp, W. Elger, Steroids 65, 2000, 741-751).

Un papel significativo de la progesterona y los receptores de progesterona también se conoce en los procesos patofisiológicos. Se han detectado receptores de progesterona en focos de endometriosis, pero también en tumores de útero, de mama y del SNC. También se sabe que los leiomiomas de útero crecen en función de la progesterona.

Los efectos de la progesterona en los tejidos de los órganos genitales y en otros tejidos se producen por interacciones con receptores de progesterona que son responsables de los efectos celulares.

Los moduladores de los receptores de progesterona son agonistas puros o bien inhiben la acción de la progesterona parcial o totalmente. Conforme a esto, las sustancias se definen como agonistas puros, agonistas parciales (SPRMS) y antagonistas puros.

Según la capacidad de los moduladores de los receptores de progesterona de influir la acción del receptor de progesterona, estos compuestos poseen un considerable potencial como agentes terapéuticos para indicaciones ginecológicas y oncológicas, así como para la obstetricia y el control de la fertilidad.

Los antagonistas puros de los receptores de progesterona inhiben por completo la acción de la progesterona en el

receptor de progesterona. Tienen propiedades anovulatorias así como la capacidad de inhibir los efectos estrogénicos en el endometrio hasta la completa atrofia. Por ello, son particularmente apropiados para intervenir en el proceso reproductivo de la mujer, por ejemplo, de modo posovulatorio para impedir la anidación, en el embarazo, para elevar la predisposición del útero a la reacción a prostaglandinas u oxitocina o para una dilatación y ablandamiento ("maduración") del cuello, así como para desencadenar una alta predisposición del miometrio a los dolores de parto.

En focos de endometriosis o bien en tejido tumoral que está(n) provistos de receptores de progesterona, se espera una influencia favorable del cuadro de la enfermedad después de la aplicación de antagonistas puros de receptores de progesterona. Si además se logra una inhibición de la ovulación por medio de antagonistas de receptores de progesterona, se podrían obtener ventajas especiales que permitan influenciar estados patológicos como endometriosis o leiomiomas de útero. Con la inhibición de la ovulación no tienen lugar una parte de la producción hormonal ovárica y, por consiguiente, el efecto de estimulación sobre el tejido patológicamente modificado que recae sobre esta parte.

Al primer antagonista de receptores de progesterona descrito, RU 486 (también mifepristona), le siguieron una gran cantidad de análogos con diferente potencia de activi-

dad antagonista de receptores de progesterona. Mientras que el RU 486 muestra también un efecto antiglucocorticoide además del efecto antagonista de receptores de progesterona, los compuestos sintetizados después se caracterizan sobre todo por una acción más selectiva como antagonistas de receptores de progesterona.

Además de compuestos esteroides como onapristona o lilopristona, que se caracterizan frente a RU 486 por una mejor disociación activa del efecto antagonista de los receptores de progesterona respecto del efecto antiglucocorticoide, a través de la literatura se conocen también diversas estructuras no esteroides cuya acción antagonista se investiga en el receptor de progesterona [ver, por ejemplo, S. A. Leonhardt y D. P. Edwards, Exp. Biol. Med. 227: 969-980 (2002) y R. Winneker, A. Fensome, J. E. Wrobel, Z. Zhang, P. Zhang, Seminars in Reproductive Medicine, Volume 23: 46-57 (2005)]. Sin embargo, los compuestos conocidos hasta la fecha sólo poseen una actividad antagonista moderada en comparación con la de las estructuras esteroides conocidas. Los compuestos no esteroides más efectivos se describen con actividades *in vitro* del 10% de la actividad de RU 486.

La actividad antiglucocorticoide es desventajosa para una aplicación terapéutica, en la que la inhibición de los receptores de progesterona está en el primer plano de la terapia. Una eficacia antiglucocorticoide produce efectos co-

laterales no deseados con las dosis requeridas en terapéutica. Esto puede impedir la aplicación de una dosis terapéuticamente conveniente o producir la interrupción del tratamiento.

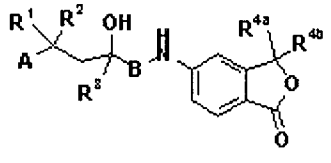
Por ello, la reducción parcial o total de las propiedades antiglucocorticoides es una importante condición para la terapia con antagonistas de receptores de progesterona, en especial para aquellas indicaciones que requieren de un tratamiento de semanas o meses.

Contrariamente a los antagonistas puros, los agonistas parciales de los receptores de progesterona (SPRM) muestran una propiedad agonista residual que puede estar caracterizada por una diferente potencia. Esto lleva a que estas sustancias exhiban, en determinados sistemas orgánicos, efectos potencialmente agonistas en el receptor de progesterona (D. DeManno, W. Elger, R. Garg, R. Lee, b. Schneider, H. Hess-Stumpp, G. Schuber, K. Chwalisz, Steroids 68, 2003, 1019-1032). Una acción específica de órganos y disociada de este tipo puede ser de utilidad terapéutica para las indicaciones descritas.

Por ello, es objeto de la presente invención poner a disposición otros moduladores no esteroides de receptores de progesterona. Estos compuestos deben poseer una acción antiglucocorticoide reducida y, por eso, son apropiados para la terapia y la prevención de enfermedades ginecológicas tales

como endometriosis, leiomiomas de útero, hemorragias disfuncionales y dismenorrea. Además, los compuestos según la invención deben ser apropiados para la terapia y la prevención de tumores dependientes de hormonas, por ejemplo, de carcinomas de mama, de endometrio, de ovario y de próstata. Los compuestos también deben ser adecuados para usar en el control de la fertilidad femenina como también en la terapia de reemplazo hormonal femenina.

El objeto se resuelve de acuerdo con la presente invención poniendo a disposición compuestos no esteroides de la fórmula general I



(I),

en donde

R^1 y R^2 son, de modo independiente entre sí, un átomo de hidrógeno, un grupo alquilo C_1-C_5 lineal o no lineal, ramificado o no ramificado, que además forma junto con el átomo de C de la cadena un anillo con un total de 3-7 miembros,

R^3 es un radical C≡C-R^a, en donde

R^a es un átomo de hidrógeno o un alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_{10}, heterocicloalquilo opcionalmente mono- o polisustituido, igual o diferente, con K o un ari-

lo o heteroarilo que opcionalmente es mono- o polisustituido, igual o diferente, con L,

K es ciano, halógeno, hidroxi, nitro, $-C(O)R^b$, CO_2R^b, $-O-R^b$, $-S-R^b$, $SO_2NR^cR^d$, $-C(O)-NR^cR^d$, $-OC(O)-NR^cR^d$, o $-C=NOR^b$ $-NR^cR^d$ o un cicloalquilo C_3-C_{10}, heterocicloalquilo opcionalmente mono- o polisustituido, igual o diferente, con M o arilo o heteroarilo opcionalmente mono- o polisustituido con L,

L es alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, perfluoroalquilo C_1-C_6, perfluoroalcoxi C_1-C_6, alcoxi C_1-C_6-alcoxi C_1-C_6, $(CH_2)_p$-cicloalquilo C_3-C_{10}, $(CH_2)_p$-heterocicloalquilo, $(CH_2)_pCN$, $(CH_2)_pHal$, $(CH_2)_pNO_2$, $(CH_2)_p$-arilo C_6-C_{12}, $(CH_2)_p$-heteroarilo,

$-(CH_2)_pPO_3(R^b)_2$,

$-(CH_2)_pNR^cR^d$, $-(CH_2)_pNR^eCOR^b$,

$-(CH_2)_pNR^eCSR^b$, $-(CH_2)_pNR^eS(O)R^b$,

$-(CH_2)_pNR^eS(O)_2R^b$,

$-(CH_2)_pNR^eCONR^cR^d$,

$-(CH_2)_pNR^eCOOR^b$,

$-(CH_2)_pNR^eC(NH)NR^cR^d$,

$-(CH_2)_pNR^eCSNR^cR^d$,

$-(CH_2)_pNR^eS(O)NR^cR^d$,

$-(CH_2)_pNR^eS(O)_2NR^cR^d$, $-(CH_2)_pCOR^b$,

$-(CH_2)_pCSR^b$, $-(CH_2)_pS(O)R^b$,

$-(CH_2)_pS(O)(NH)R^b$, $-(CH_2)_pS(O)_2R^b$,

$-(CH_2)_pS(O)_2NR^cR^d$, $-(CH_2)_pSO_2OR^b$,

$-(CH_2)_pCO_2R^b$, $-(CH_2)_pCONR^cR^d$,

$-(CH_2)_pCSNR^cR^d$, $-(CH_2)_pOR^b$,

$-(CH_2)_pSR^b$, $-(CH_2)_pCR^b(OH)-R^e$,

$-(CH_2)_p-C=NOR^b$, $-O-(CH_2)_n-O-$, $-O-(CH_2)_n-CH_2-$, $-O-CH=CH-$ o $-(CH_2)_{n+2}-$, en donde es n = 1 ó 2 y los átomos de oxígeno y/o átomos de carbono terminales están unidos con átomos de carbono del anillo directamente adyacentes,

M es alquilo C_1-C_6 o un grupo $-COR^b$, CO_2R^b, $-O-R^b$ o $-NR^cR^d$, en donde

R^b es un átomo de hidrógeno o alquilo C_1-C_6, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_{10}, arilo C_6-C_{12} o perfluoroalquilo C_1-C_3 y

R^c y R^d son, de modo independiente entre sí, un átomo de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_{10}, arilo C_6-C_{12}, $C(O)R^b$ o un grupo hidroxi, en donde cuando

R^c es un grupo hidroxi, R^d sólo puede ser un átomo de hidrógeno, un alquilo C_1-C_6, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_{10} o arilo C_6-C_{12}, y viceversa, así como

R^e es un átomo de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_{10} o arilo C_6-C_{12} y

p puede ser una cifra de 0 a 6,

o

R^3 es un radical $C{=}C\text{-}R^gR^h$, en donde

R^g y R^h son de modo independiente entre sí, un átomo de hidrógeno o un alquilo C_1-C_8, alquenilo C_2-C_8 o alquinilo C_2-C_8 opcionalmente mono- o polisustituido, igual o diferente, con X, en donde

X es ciano, halógeno, hidroxi, nitro, $-C(O)R^b$, CO_2R^b, $-O-R^b$, $-C(O)-NR^cR^d$, $-NR^cR^d$ con los significados ya mencionados más arriba para R^b, R^c y R^d y

R^{4a} y R^{4b} son, de modo independiente entre sí, un átomo de hidrógeno, un alquilo C_1-C_4, un alquenilo C_2-C_4 o forman, junto con el átomo de carbono del anillo, un anillo de 3-6 miembros,

A es un anillo aromático carbocíclico o heterocíclico mono- o bicíclico, que puede estar opcionalmente mono- o polisustituido con alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, perfluoroalquilo C_1-C_6, perfluoroalcoxi C_1-C_6, alcoxi C_1-C_6-alquilo C_1-C_6, alcoxi C_1-C_6-alcoxi C_1-C_6, $(CH_2)_p$-cicloalquilo C_3-C_{10}, $(CH_2)_p$-

heterocicloalquilo, $(CH_2)_pCN$, $(CH_2)_pHal$, $(CH_2)_pNO_2$, $(CH_2)_p$-arilo C_6-C_{12}, $(CH_2)_p$-heteroarilo, $-(CH_2)_pPO_3(R^b)_2$, $-(CH_2)_pNR^cR^d$, $-(CH_2)_pNR^eCOR^b$, $-(CH_2)_pNR^eCSR^b$, $-(CH_2)_pNR^eS(O)R^b$, $-(CH_2)_pNR^eS(O)_2R^b$, $-(CH_2)_pNR^eCONR^cR^d$, $-(CH_2)_pNR^eCOOR^b$, $-(CH_2)_pNR^eC(NH)NR^cR^d$, $-(CH_2)_pNR^eCSNR^cR^d$, $-(CH_2)_pNR^eS(O)NR^cR^d$, $-(CH_2)_pNR^eS(O)_2NR^cR^d$, $-(CH_2)_pCOR^b$, $-(CH_2)_pCSR^b$, $-(CH_2)_p$ $S(O)R^b$, $-(CH_2)_pS(O)(NH)R^b$, $-(CH_2)_pS(O)_2R^b$, $-(CH_2)_pS(O)_2NR^cR^d$, $-(CH_2)_pSO_2OR^b$, $-(CH_2)_pCO_2R^b$, $-(CH_2)_pCONR^cR^d$, $-(CH_2)_pCSNR^cR^d$, $-(CH_2)_pOR^b$, $-(CH_2)_pSR^b$, $-(CH_2)_pCR^b(OH)-R^d$, $-(CH_2)_p-C=NOR^b$, $-O-(CH_2)_n-O-$, $-O-(CH_2)_n-CH_2-$, $-O-CH=CH-$ o $-(CH_2)_{n+2}-$, en donde es n = 1 ó 2 y los átomos de oxígeno y/o átomos de carbono están unidos con átomos de carbono del anillo directamente adyacentes o

A es un radical $-CO_2R^b$, $C(O)NR^cR^d$, COR^b,

o

A es un grupo alquenilo $-CR^5=CR^6R^7$, en donde R^5, R^6 y R^7 son iguales o diferentes y son, de modo independiente entre sí, átomos de hidrógeno, átomos de halógeno, radicales arilo o un grupo alquilo C_1-C_5 no sustituido o parcial o totalmente fluorado o

A es un grupo alquinilo $-C\equiv CR^5$, con el significado indicado arriba para R^5 y

B es un grupo carbonilo o un grupo CH_2,

así como sus sales farmacéuticamente aceptables.

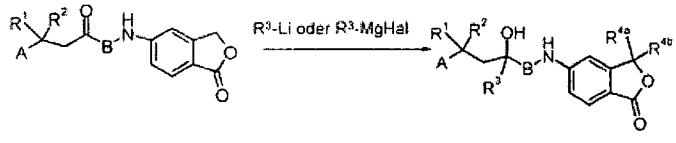
Los compuestos según la invención de la fórmula general I pueden existir como diferentes estereoisómeros por la presencia de centros de asimetría. Tanto el uso de los racematos, como también el de los estereoisómeros que existen por separado pertenecen al objeto de la presente invención.

Además, la presente invención comprende los nuevos compuestos como principios activos farmacéuticos, su preparación, su aplicación terapéutica y sus formas de administración farmacéutica que contienen las nuevas sustancias.

Los compuestos según la invención de la fórmula general (I) o sus sales farmacéuticamente aceptables se pueden usar para la preparación de un agente farmacéutico, en especial para el tratamiento y la prevención de enfermedades ginecológicas tales como endometriosis, leiomiomas de útero, hemorragias disfuncionales y dismenorrea. Además, los compuestos según la invención para el tratamiento y la profilaxis de tumores dependientes de hormonas, tales como, por ejemplo, para carcinoma de mama, de próstata y de endometrio.

Los compuestos según la invención de la fórmula general (I) o sus sales farmacéuticamente aceptables son apropiados para usar en el control de la fertilidad femenina o para la terapia de reemplazo hormonal femenino.

Más aun, también constituye un objeto de la invención un proceso para la producción de los compuestos de la fórmula general (I. El sustituyente R^3 se introduce en un grupo ceto por reacción de adición selectiva de compuestos organometálicos tales como litio alquinileno o magnesio haloalquinileno. Esto resulta de manera directa o luego de la implementación de modificaciones adicionales, en los compuestos de la fórmula general (I) de acuerdo con la invención.



(o)

...La producción de los compuestos de acuerdo con la invención se realiza por adición selectiva de compuestos organometálicos a cetoamidas, por ejemplo tal como se describió en la memoria descriptiva abierta de WO 200375915 y WO 9854159. Los compuestos organometálicos pueden ser, por ejemplo, compuestos de litio alquinilo o compuestos de magnesio haloalquinilo. Estos últimos son producidos, por ejemplo, por reacción de las correspondientes alquinas con compuestos de Grignard o butil-litio. Es posible producir de manera análoga los correspondientes compuestos alquenilo organometálicos. La reactividad del grupo ceto en comparación con amidocarbonilo o ftalida es, en este caso, significativamente más elevada de manera que con una selección apropiada de las

condiciones de reacción , se logra una adición selectiva. Como alternativa, también es posible modificar posteriormente los radicales alquinilo o alquenilo que se introducen como R3. Para estas modificaciones, resultan apropiadas las reacciones que se han tornado conocidas para los expertos en la técnica tal como oxidación , reducción, sustitución, alquilación, o reacción catalizada por paladio. De manera opcional, se separan los grupos protectores presentan en un momento apropiado.

Los compuestos no esteroides de la fórmula general I según la invención actúan de modo fuertemente antagonista o parcialmente agonista en el receptor de progesterona. Presentan una fuerte disociación de acción en lo que respecta a su fuerza de unión con el receptor de progesterona y de glucocorticoide. Mientras que los conocidos antagonistas del receptor de progesterona como mifepristona (RU 486) muestran, además de la gran afinidad de unión con el receptor de progesterona deseada, asimismo una gran afinidad por el receptor de glucocorticoide, los compuestos según la invención se caracterizan por una unión muy pequeña con el receptor de glucocorticoide con una gran afinidad simultáneamente existente con el receptor de progesterona.

Los sustituyentes de los compuestos de la fórmula general I según la invención definidos como grupos tienen los siguientes significados:

Por grupo alquilo C_1-C_5, C_1-C_6 o C_1-C_8 se entienden radicales alquilo lineales o no lineales, ramificados o no ramificados. En este caso se trata, p.ej., de un grupo metilo, etilo, n-propilo, iso-propilo, n-, iso-, ter.-butilo-, n-pentilo, 2,2-dimetilpropilo, 3-metilbutilo, hexilo, heptilo u octilo.

En el sentido de R^a, se prefieren en este caso los grupos metilo, etilo, n-propilo o n-butilo, así como un grupo n-pentilo.

En el sentido de R^1 y R^2, se prefieren metilo o etilo.

Según la invención, para R^{4a} y R^{4b} se prefiere un átomo de hidrógeno.

Por alquenilo se entienden radicales alquenilo lineales o no lineales, ramificados o no ramificados. En el sentido de la invención, se entienden por grupo alquenilo C_2-C_8, por ejemplo, los siguientes: vinilo, alilo, 3-buten-1-ilo o 2,3-dimetil-2-propenilo. Si el compuesto aromático A está sustituido con un radical alquenilo C_2-C_8, se trata preferentemente de un grupo vinilo.

Por alquinilo se entienden radicales alquinilo lineales o no lineales, ramificados o no ramificados. Son un radical alquinilo C_2-C_8, por ejemplo, un grupo etinilo, propinilo, butinilo, pentinilo, hexinilo, así como octinilo, pero con preferencia un grupo etinilo o propinilo.

Para cicloalquilo C_3-C_{10} se mencionan, a modo de ejemplo, ciclopropano, ciclobutano, ciclopentano y ciclohexano. Se prefieren ciclopropilo, ciclopentilo y ciclohexilo.

Por heterocicloalquilo en el sentido de R^a, K o bien L se entienden radicales heterocicloalquilo de 3-8 miembros. Ejemplos de heterocicloalquilo son morfolina, tetrahidrofurano, pirano, piperazina, piperidina, pirrolidina, oxirano, oxetano, aziridina, dioxolano y dioxano. En este caso, la posición del heteroátomo en relación con el sitio de unión puede ser cualquier posición químicamente posible.

Un grupo alcoxil C_1-C_6-alcoxi C_1-C_6 puede ser, por ejemplo, metoximetoxi, etoximetoxi o 2-metoxietoxi.

En el caso de un radical OR^b se trata, en el sentido de la invención, de un grupo hidroxi, metoxi, etoxi, n-propoxi, iso-propoxi, n-, iso-, ter.-butoxi o n-pentoxi, 2,2-dimetilpropoxi o 3-metilbutoxi. Se prefieren hidroxi, metoxi y etoxi.

Para un grupo alquilo C_1-C_5 parcial o totalmente fluorado se tienen en cuenta los grupos alquilo perfluorados anteriores. De ellos se prefieren, sobre todo, los grupos trifluorometilo o pentafluoroetilo, y como grupos alquilo parcialmente fluorados, por ejemplo, se prefieren los grupos 5,5,4,4-pentafluoropentilo o 5,5,5,4,4,3,3-heptafluoropentilo.

Un átomo de halógeno puede ser un átomo de flúor, cloro, bromo o yodo. Aquí se prefiere flúor, cloro o bromo.

Cuando R^1 y R^2 forman junto con el átomo de C de la cadena un anillo de 3-7 miembros, éste será por ejemplo un anillo ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo. Se prefieren tanto el anillo ciclopropilo como el anillo ciclopentilo.

El anillo A aromático carbocíclico mono- o bicíclico, que puede estar polisustituido, es un radical arilo carbocíclico o heterocíclico.

En el primer caso, se trata p.ej. de un radical fenilo o naftilo, con preferencia de un radical fenilo.

Como radical heterocíclico se puede usar, por ejemplo, un radical heterocíclico monocíclico, por ejemplo, el radical tienilo, furilo, piranilo, pirrolilo, imidazolilo, pirazolilo, piridilo, pirazinilo, pirimidinilo, piridazinilo, tiazolilo, oxazolilo, furazanilo, pirrolinilo, imidazolinilo, pirazolinilo, tiazolinilo, triazolilo, tetrazolilo, para ser precisos, todos los posibles isómeros respecto de las posiciones de los heteroátomos.

En el sentido de R^3, se trata en el caso de un radical arilo de un radical fenilo, 1- o 2-naftilo opcionalmente sustituido, prefiriendo el radical fenilo. Ejemplos de un radical heteroarilo son el radical 2-, 3- o 4-piridinilo, 2- o 3-furilo, 2- o 3-tienilo, 2- o 3-pirrolilo, 2-, 4- o 5-

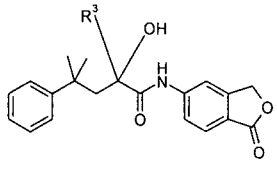
imidazolilo, pirazinilo, 2-, 4- o 5-pirimidinilo o 3- o 4-piridazinilo.

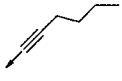
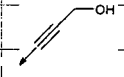
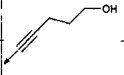
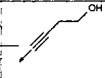
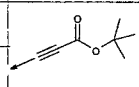
La cifra p para el radical $(CH_2)_p$ puede ser un número de 0 a 6, con preferencia de 0 a 2. Por "radical" se entienden según la invención todos los grupos funcionales que se enuncian en combinación con $(CH_2)_p$.

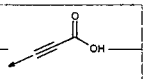
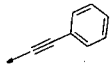
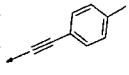
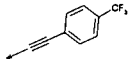
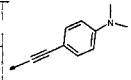
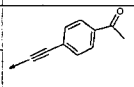
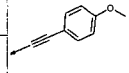
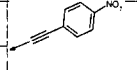
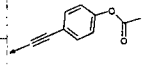
En el caso de que los compuestos de la fórmula general I (B = $-CH_2-$) estén presentes como sales, esto puede ser, por ejemplo, en forma de clorhidrato, sulfato, nitrato, tartrato, citrato, fumarato, succinato o benzoato.

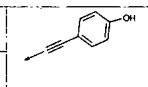
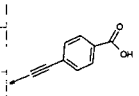
Cuando los compuestos según la invención están presentes como mezclas racémicas, se pueden separar, según métodos de separación de racematos usuales para el especialista, en las formas puras ópticamente activas. A modo de ejemplo, las mezclas racémicas se separan en los isómeros puros por cromatografía en un material de soporte ópticamente activo en sí (CHIRALPAK AD®). También es posible esterificar el grupo hidroxi libre en un compuesto racémico de la fórmula general I con un ácido ópticamente activo y separar los ésteres diastereoisoméricos obtenidos por cristalización por fraccionamiento o por cromatografía y saponificar los ésteres separados en cada uno de los isómeros ópticamente puros. Como ácidos ópticamente activos se pueden usar, por ejemplo, ácido mandélico, ácido canfersulfónico o ácido tartárico.

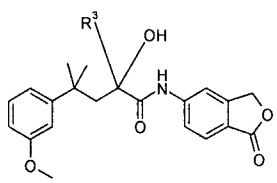
Los compuestos mencionados más adelante y su uso se prefieren según la invención:

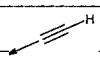
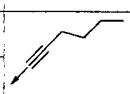
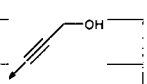
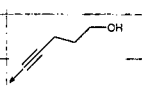
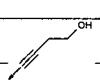


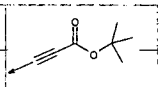
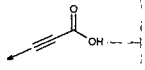
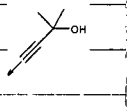
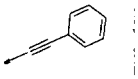
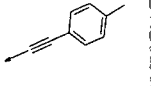
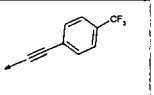
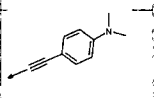
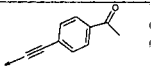
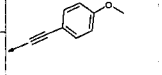
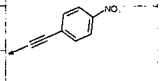
N.°	Racémico o enantiómero	R3
1	rac	
2	+	
3	–	
4	rac	
5	+	
6	–	
7	rac	
8	+	
9	–	
10	rac	
11	+	
12	–	
13	rac	
14	+	
15	–	
16	rac	
17	+	
18	–	
19	rac	
20	+	
21	–	
22	rac	
23	+	
24	–	

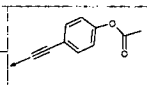
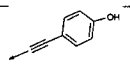
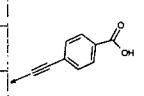
25	rac	
26	+	
27	–	
28	rac	
29	+	
30	–	
31	rac	
32	+	
33	–	
34	rac	
35	+	
36	–	
37	rac	
38	+	
39	–	
40	rac	
41	+	
42	–	
43	rac	
44	+	
45	–	
46	rac	
47	+	
48	–	
49	rac	
50	+	
51	–	
52	rac	
53	+	
54	–	

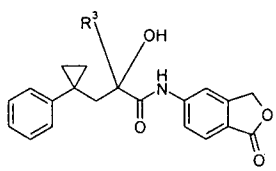
55	rac	
56	+	
57	–	
58	rac	
59	+	
60	–	

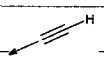
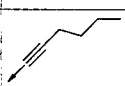
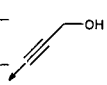
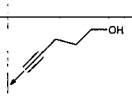


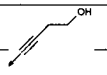
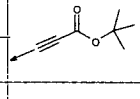
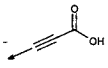
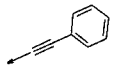
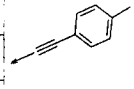
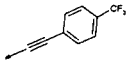
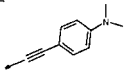
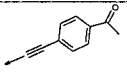
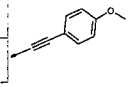
N.°	Racémico o enantiómero	R3
61	rac	
62	+	
63	–	
64	rac	
65	+	
66	–	
67	rac	
68	+	
69	–	
70	rac	
71	+	
72	–	
73	rac	
74	+	
75	–	
76	rac	
77	+	
78	–	
79	rac	
80	+	
81	–	

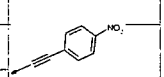
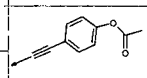
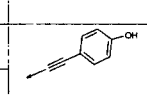
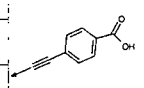
82	rac	
83	+	
84	–	
85	rac	
86	+	
87	–	
88	rac	
89	+	
90	–	
91	rac	
92	+	
93	–	
94	rac	
95	+	
96	–	
97	rac	
98	+	
99	–	
100	rac	
101	+	
102	–	
103	rac	
104	+	
105	–	
106	rac	
107	+	
108	–	
109	rac	
110	+	
111	–	

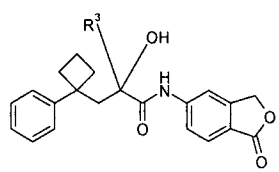
112	rac	
113	+	
114	-	
115	rac	
116	+	
117	-	
118	rac	
119	+	
120	-	

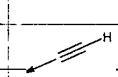
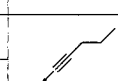
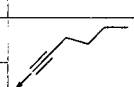
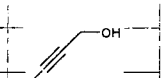


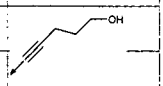
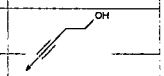
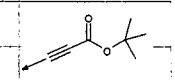
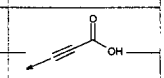
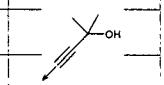
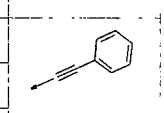
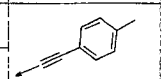
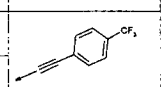
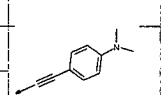
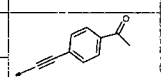
N.°	Racémico o enantiómero	R3
121	rac	
122	+	
123	-	
124	rac	
125	+	
126	-	
127	rac	
128	+	
129	-	
130	rac	
131	+	
132	-	
133	rac	
134	+	
135	-	
136	rac	
137	+	

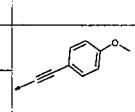
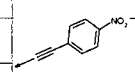
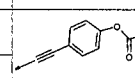
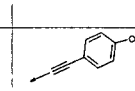
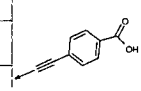
138	–	
139	rac	
140	+	
141	–	
142	rac	
143	+	
144	–	
145	rac	
146	+	
147	–	
148	rac	
149	+	
150	–	
151	rac	
152	+	
153	–	
154	rac	
155	+	
156	–	
157	rac	
158	+	
159	–	
160	rac	
161	+	
162	–	
163	rac	
164	+	
165	–	
166	rac	
167	+	

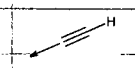
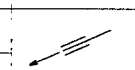
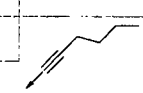
168	–	
169	rac	
170	+	
171	–	
172	rac	
173	+	
174	–	
175	rac	
176	+	
177	–	
178	rac	
179	+	
180	–	

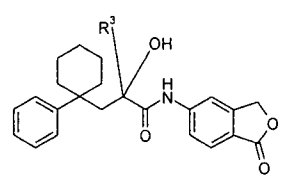


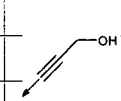
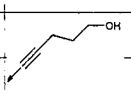
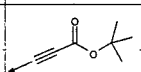
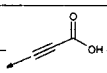
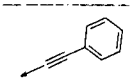
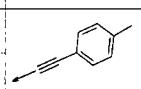
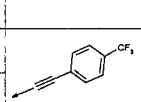
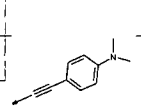
N.°	Racémico o enantiómero	R3
181	rac	
182	+	
183	–	
184	rac	
185	+	
186	–	
187	rac	
188	+	
189	–	
190	rac	
191	+	
192	–	
193	rac	
194	+	

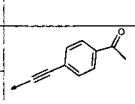
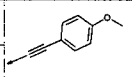
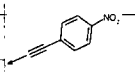
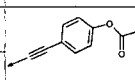
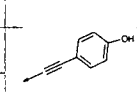
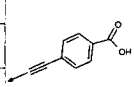
195	–	
196	rac	
197	+	
198	–	
199	rac	
200	+	
201	–	
202	rac	
203	+	
204	–	
205	rac	
206	+	
207	–	
208	rac	
209	+	
210	–	
211	rac	
212	+	
213	–	
214	rac	
215	+	
216	–	
217	rac	
218	+	
219	–	
220	rac	
221	+	
222	–	
223	rac	
224	+	

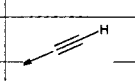
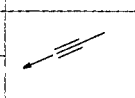
225	–	
226	rac	
227	+	
228	–	
229	rac	
230	+	
231	–	
232	rac	
233	+	
234	–	
235	rac	
236	+	
237	–	
238	rac	
239	+	
240	–	

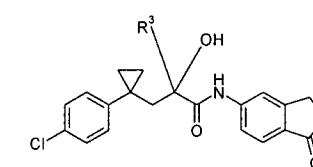
N.°	Racémico o enantiómero	R3
241	rac	
242	+	
243	–	
244	rac	
245	+	
246	–	
247	rac	
248	+	
249	–	
250	rac	

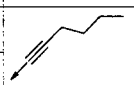
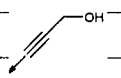
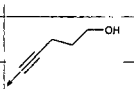
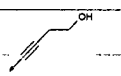
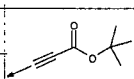
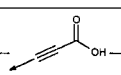
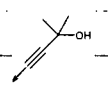
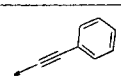
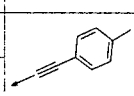
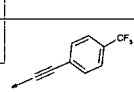


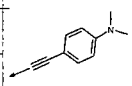
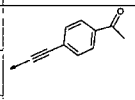
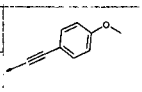
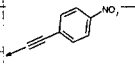
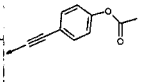
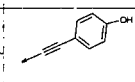
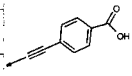
251	+	
252	–	
253	rac	
254	+	
255	–	
256	rac	
257	+	
258	–	
259	rac	
260	+	
261	–	
262	rac	
263	+	
264	–	
265	rac	
266	+	
267	–	
268	rac	
269	+	
270	–	
271	rac	
272	+	
273	–	
274	rac	
275	+	
276	–	
277	rac	
278	+	
279	–	
280	rac	

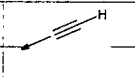
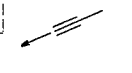
281	+	
282	-	
283	rac	
284	+	
285	-	
286	rac	
287	+	
288	-	
289	rac	
290	+	
291	-	
292	rac	
293	+	
294	-	
295	rac	
296	+	
297	-	
298	rac	
299	+	
300	-	

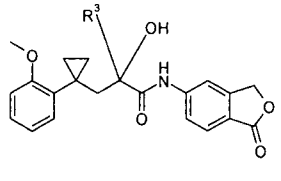
N.°	Racémico o enantiómero	R3
301	rac	
302	+	
303	-	
304	rac	
305	+	
306	-	
307	rac	

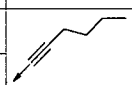
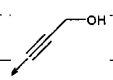
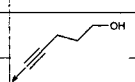
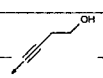
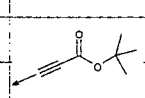
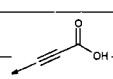
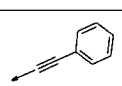
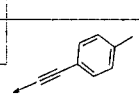


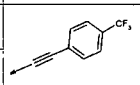
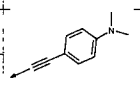
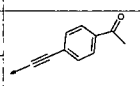
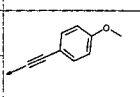
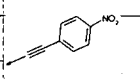
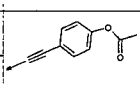
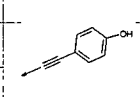
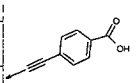
308	+	
309	–	
310	rac	
311	+	
312	–	
313	rac	
314	+	
315	–	
316	rac	
317	+	
318	–	
319	rac	
320	+	
321	–	
322	rac	
323	+	
324	–	
325	rac	
326	+	
327	–	
328	rac	
329	+	
330	–	
331	rac	
332	+	
333	–	
334	rac	
335	+	
336	–	
337	rac	

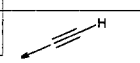
338	+	
339	–	
340	rac	
341	+	
342	–	
343	rac	
344	+	
345	–	
346	rac	
347	+	
348	–	
349	rac	
350	+	
351	–	
352	rac	
353	+	
354	–	
355	rac	
356	+	
357	–	
358	rac	
359	+	
360	–	

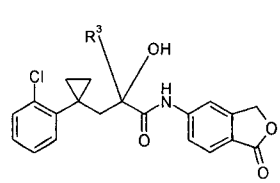
N.º	Racémico o enantiómero	R3
361	rac	
362	+	
363	–	
364	rac	

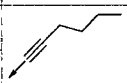
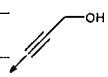
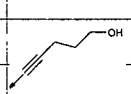
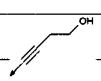
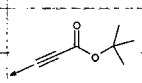
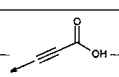
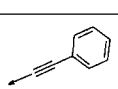


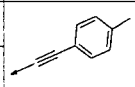
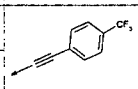
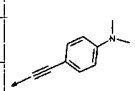
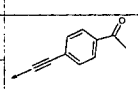
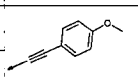
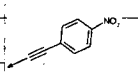
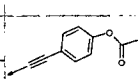
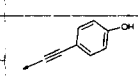
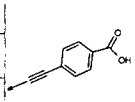
365	+	
366	–	
367	rac	
368	+	
369	–	
370	rac	
371	+	
372	–	
373	rac	
374	+	
375	–	
376	rac	
377	+	
378	–	
379	rac	
380	+	
381	–	
382	rac	
383	+	
384	–	
385	rac	
386	+	
387	–	
388	rac	
389	+	
390	–	
391	rac	
392	+	
393	–	
394	rac	

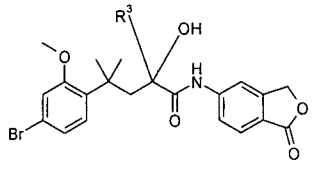
395	+	
396	-	
397	rac	
398	+	
399	-	
400	rac	
401	+	
402	-	
403	rac	
404	+	
405	-	
406	rac	
407	+	
408	-	
409	rac	
410	+	
411	-	
412	rac	
413	+	
414	-	
415	rac	
416	+	
417	-	
418	rac	
419	+	
420	-	

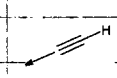
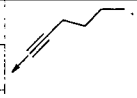
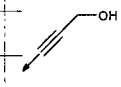
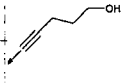
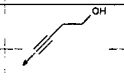
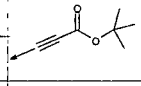
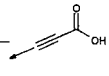
N.°	Racémico o enantiómero	R3
421	rac	

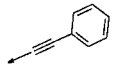
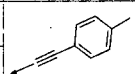
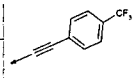
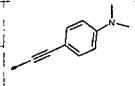
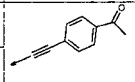
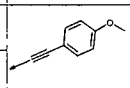
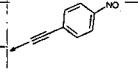
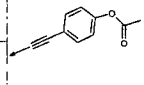
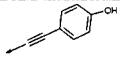
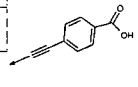


422	+	
423	–	
424	rac	
425	+	
426	–	
427	rac	
428	+	
429	–	
430	rac	
431	+	
432	–	
433	rac	
434	+	
435	–	
436	rac	
437	+	
438	–	
439	rac	
440	+	
441	–	
442	rac	
443	+	
444	–	
445	rac	
446	+	
447	–	
448	rac	
449	+	
450	–	
451	rac	

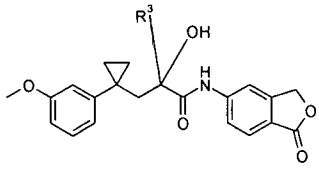
452	+	
453	-	
454	rac	
455	+	
456	-	
457	rac	
458	+	
459	-	
460	rac	
461	+	
462	-	
463	rac	
464	+	
465	-	
466	rac	
467	+	
468	-	
469	rac	
470	+	
471	-	
472	rac	
473	+	
474	-	
475	rac	
476	+	
477	-	
478	rac	
479	+	
480	-	

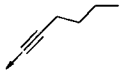
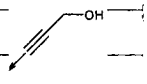
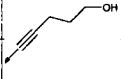
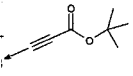
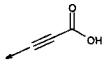


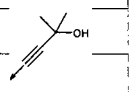
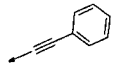
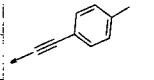
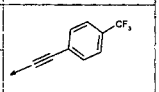
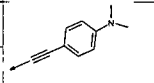
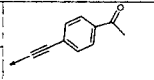
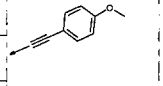
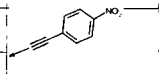
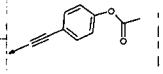
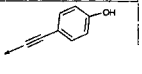
N.°	Racémico o enantiómero	R3
481	rac	
482	+	
483	–	
484	rac	
485	+	
486	–	
487	rac	
488	+	
489	–	
490	rac	
491	+	
492	–	
493	rac	
494	+	
495	–	
496	rac	
497	+	
498	–	
499	rac	
500	+	
501	–	
502	rac	
503	+	
504	–	
505	rac	
506	+	
507	–	
508	rac	

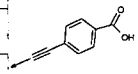
509	+	
510	–	
511	rac	
512	+	
513	–	
214	rac	
515	+	
516	–	
517	rac	
518	+	
519	–	
520	rac	
521	+	
522	–	
523	rac	
524	+	
525	–	
526	rac	
227	+	
528	–	
529	rac	
530	+	
531	–	
532	rac	
533	+	
534	–	
535	rac	
536	+	
537	–	
538	rac	

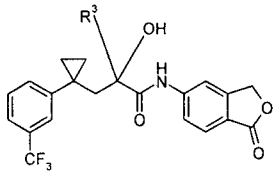
539	+
540	–

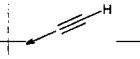
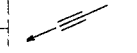
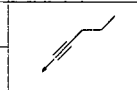
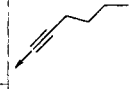
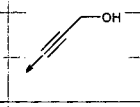
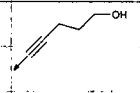
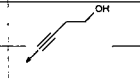


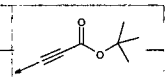
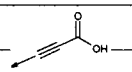
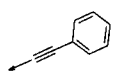
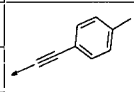
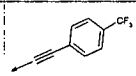
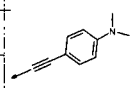
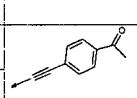
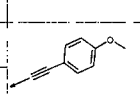
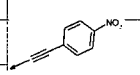
N.°	Racémico o enantiómero	R3
541	rac	
542	+	
543	–	
544	rac	
545	+	
546	–	
547	rac	
548	+	
549	–	
550	rac	
551	+	
552	–	
553	rac	
554	+	
555	–	
556	rac	
557	+	
558	–	
559	rac	
560	+	
561	–	
562	rac	
563	+	
564	–	
565	rac	

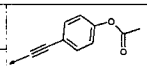
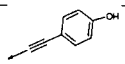
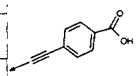
566	+	
567	–	
568	rac	
569	+	
570	–	
571	rac	
572	+	
573	–	
574	rac	
575	+	
576	–	
577	rac	
578	+	
579	–	
580	rac	
581	+	
582	–	
583	rac	
584	+	
585	–	
586	rac	
587	+	
588	–	
589	rac	
590	+	
591	–	
592	rac	
593	+	
594	–	
595	rac	

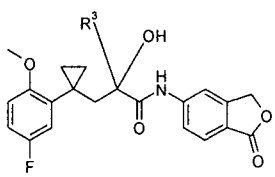
596	+	
597	–	
598	rac	
599	+	
600	–	

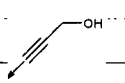
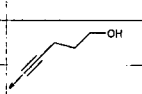


N.°	Racémico o enantiómero	R3
601	rac	
602	+	
603	–	
604	rac	
605	+	
606	–	
607	rac	
608	+	
609	–	
610	rac	
611	+	
612	–	
613	rac	
614	+	
615	–	
616	rac	
617	+	
618	–	
619	rac	
620	+	
621	–	

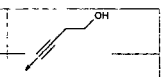
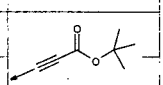
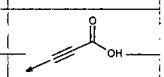
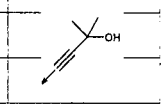
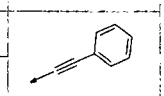
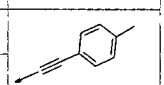
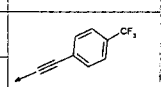
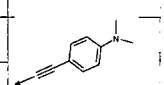
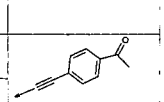
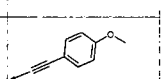
622	rac	
623	+	
624	–	
625	rac	
626	+	
627	–	
628	rac	
629	+	
630	–	
631	rac	
632	+	
633	–	
634	rac	
635	+	
636	–	
637	rac	
638	+	
639	–	
640	rac	
641	+	
642	–	
643	rac	
644	+	
645	–	
646	rac	
647	+	
648	–	
649	rac	
650	+	
651	–	

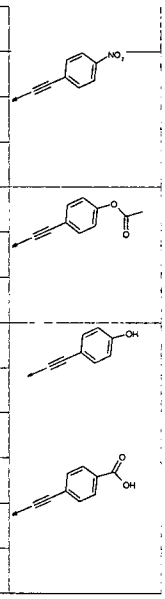
652	rac	
653	+	
654	-	
655	rac	
656	+	
657	-	
658	rac	
659	+	
660	-	

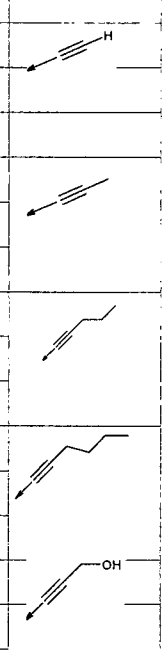


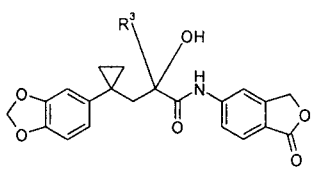
N.°	Racémico o enantiómero	R3
661	rac	
662	+	
663	-	
664	rac	
665	+	
666	-	
667	rac	
668	+	
669	-	
670	rac	
671	+	
672	-	
673	rac	
674	+	
675	-	
676	rac	
677	+	
678	-	

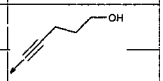
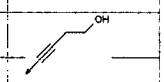
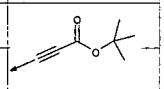
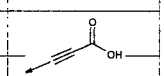
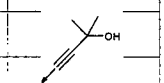
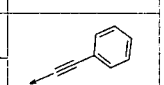
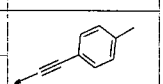
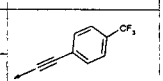
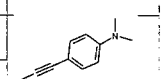
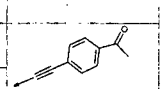
290

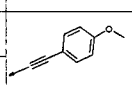
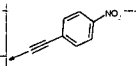
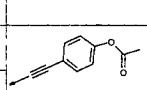
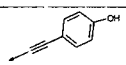
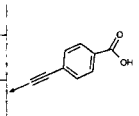
679	rac	
680	+	
681	–	
682	rac	
683	+	
684	–	
685	rac	
686	+	
687	–	
688	rac	
689	+	
690	–	
691	rac	
692	+	
693	–	
694	rac	
695	+	
696	–	
697	rac	
698	+	
699	–	
700	rac	
701	+	
702	–	
703	rac	
704	+	
705	–	
706	rac	
707	+	

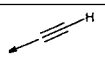
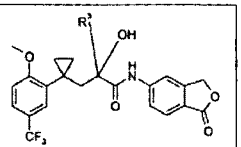
708	–	
709	rac	
710	+	
711	–	
712	rac	
713	+	
714	–	
715	rac	
716	+	
717	–	
718	rac	
719	+	
720	–	

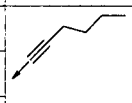
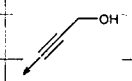
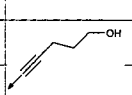
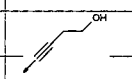
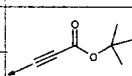
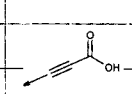
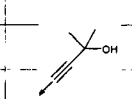
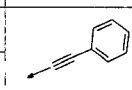
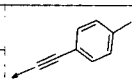
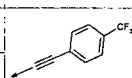
N.°	Racémico o enantiómero	R3
721	rac	
722	+	
723	–	
724	rac	
725	+	
726	–	
727	rac	
728	+	
729	–	
730	rac	
731	+	
732	–	
733	rac	
734	+	

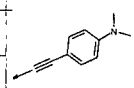
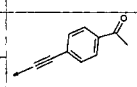
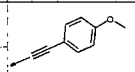
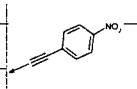
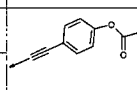
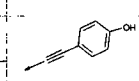
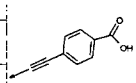


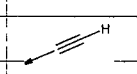
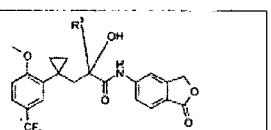
735	-	
736	rac	
737	+	
738	-	
739	rac	
740	+	
741	-	
742	rac	
743	+	
744	-	
745	rac	
746	+	
747	-	
748	rac	
749	+	
750	-	
751	rac	
752	+	
753	-	
754	rac	
755	+	
756	-	
757	rac	
758	+	
759	-	
760	rac	
761	+	
762	-	
763	rac	
764	+	

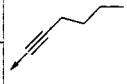
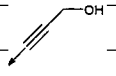
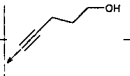
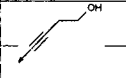
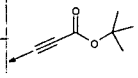
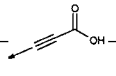
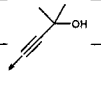
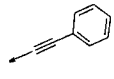
765	-	
766	rac	
767	+	
768	-	
769	rac	
770	+	
771	-	
772	rac	
773	+	
774	-	
775	rac	
776	+	
777	-	
778	rac	
779	+	
780	-	

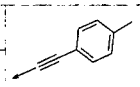
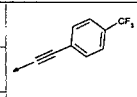
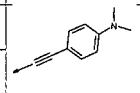
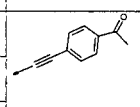
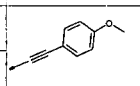
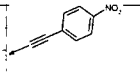
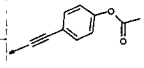
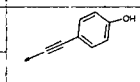
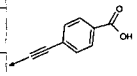
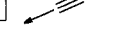
N.°	Racémico o enantiómero	R3	
781	rac		
782	+		
783	-		
784	rac		
785	+		
786	-		
787	rac		
788	+		

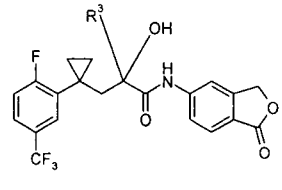
789	–	
790	rac	
791	+	
792	–	
793	rac	
794	+	
795	–	
796	rac	
797	+	
798	–	
799	rac	
800	+	
801	–	
802	rac	
803	+	
804	–	
805	rac	
806	+	
807	–	
808	rac	
809	+	
810	–	
811	rac	
812	+	
813	–	
814	rac	
815	+	
816	–	
817	rac	
818	+	

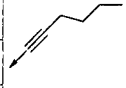
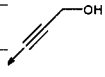
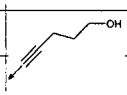
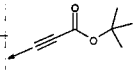
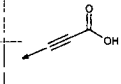
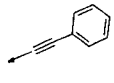
819	–	
820	rac	
821	+	
822	–	
823	rac	
824	+	
825	–	
826	rac	
827	+	
828	–	
829	rac	
830	+	
831	–	
832	rac	
833	+	
834	–	
835	rac	
836	+	
837	–	
838	rac	
839	+	
840	–	

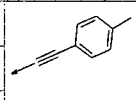
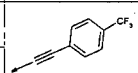
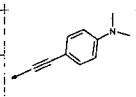
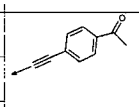
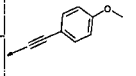
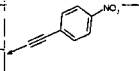
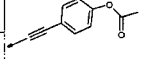
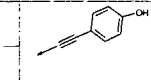
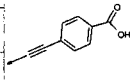
N.°	Racémico o enantiómero	R3	
841	rac		
842	+		
843	–		

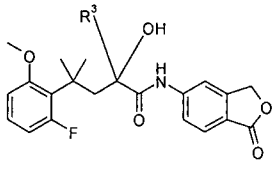
844	rac	
845	+	
846	–	
847	rac	
848	+	
849	–	
850	rac	
851	+	
852	–	
853	rac	
854	+	
855	–	
856	rac	
857	+	
858	–	
859	rac	
860	+	
861	–	
862	rac	
863	+	
864	–	
865	rac	
866	+	
867	–	
868	rac	
869	+	
870	–	
871	rac	
872	+	
873	–	

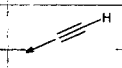
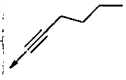
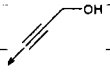
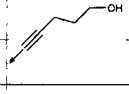
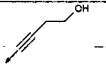
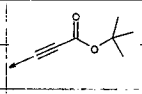
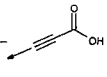
874	rac	
875	+	
876	–	
877	rac	
878	+	
879	–	
880	rac	
881	+	
882	–	
883	rac	
884	+	
885	–	
886	rac	
887	+	
888	–	
889	rac	
890	+	
891	–	
892	rac	
893	+	
894	–	
895	rac	
896	+	
897	–	
898	rac	
899	+	
900	–	
N.°	Racémico o enantiómero	R3
901	rac	

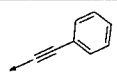
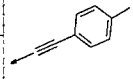
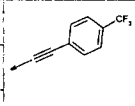
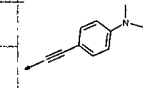
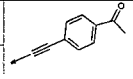
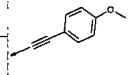
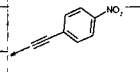
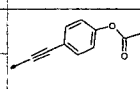
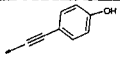
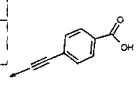


902	+	
903	–	
904	rac	
905	+	
906	–	
907	rac	
908	+	
909	–	
910	rac	
911	+	
912	–	
913	rac	
914	+	
915	–	
916	rac	
917	+	
918	–	
919	rac	
920	+	
921	–	
922	rac	
923	+	
924	–	
925	rac	
926	+	
927	–	
928	rac	
929	+	
930	–	
931	rac	

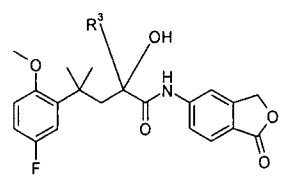
932	+	
933	–	
934	rac	
935	+	
936	–	
937	rac	
938	+	
939	–	
940	rac	
941	+	
942	–	
943	rac	
944	+	
945	–	
946	rac	
947	+	
948	–	
949	rac	
950	+	
951	–	
952	rac	
953	+	
954	–	
955	rac	
956	+	
957	–	
958	rac	
959	+	
960	–	

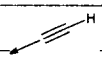
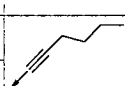
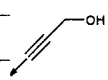
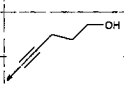
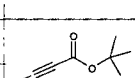
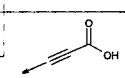


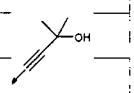
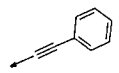
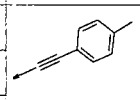
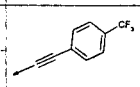
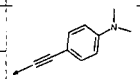
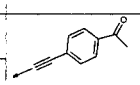
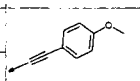
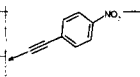
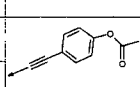
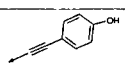
N.º	Racémico o enantiómero	R3
961	rac	
962	+	
963	-	
964	rac	
965	+	
966	-	
967	rac	
968	+	
969	-	
970	rac	
971	+	
972	-	
973	rac	
974	+	
975	-	
976	rac	
977	+	
978	-	
979	rac	
980	+	
981	-	
982	rac	
983	+	
984	-	
985	rac	
986	+	
987	-	
988	rac	

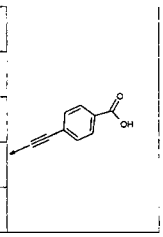
989	+	
990	–	
991	rac	
992	+	
993	–	
994	rac	
995	+	
996	–	
997	rac	
998	+	
999	–	
1000	rac	
1001	+	
1002	–	
1003	rac	
1004	+	
1005	–	
1006	rac	
1007	+	
1008	–	
1009	rac	
1010	+	
1011	–	
1012	rac	
1013	+	
1014	–	
1015	rac	
1016	+	
1017	–	
1018	rac	

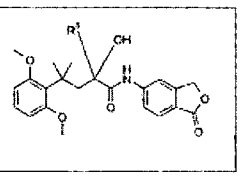
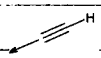
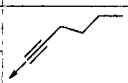
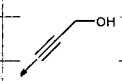
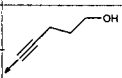
1019	+
1020	-

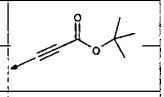
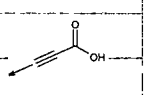
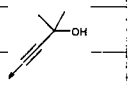
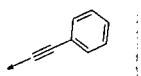
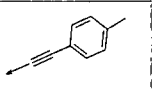
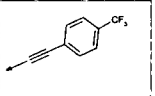
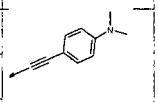
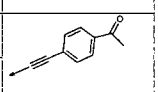
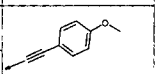
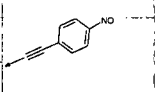


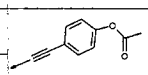
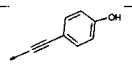
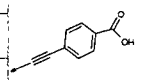
N.°	Racémico o enantiómero	R3
1021	rac	
1022	+	
1023	-	
1024	rac	
1025	+	
1026	-	
1027	rac	
1028	+	
1029	-	
1030	rac	
1031	+	
1032	-	
1033	rac	
1034	+	
1035	-	
1036	rac	
1037	+	
1038	-	
1039	rac	
1040	+	
1041	-	
1042	rac	
1043	+	
1044	-	
1045	rac	

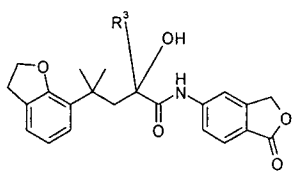
1046	+	
1047	–	
1048	rac	
1049	+	
1050	–	
1051	rac	
1052	+	
1053	–	
1054	rac	
1055	+	
1056	–	
1057	rac	
1058	+	
1059	–	
1060	rac	
1061	+	
1062	–	
1063	rac	
1064	+	
1065	–	
1066	rac	
1067	+	
1068	–	
1069	rac	
1070	+	
1071	–	
1072	rac	
1073	+	
1074	–	
1075	rac	

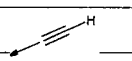
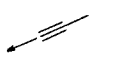
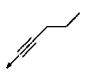
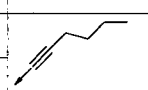
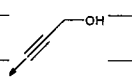
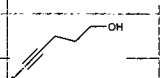
1076	+	
1077	-	
1078	rac	
1079	+	
1080	-	

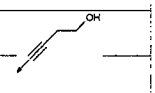
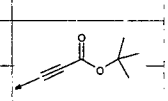
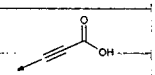
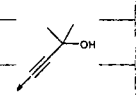
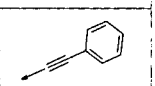
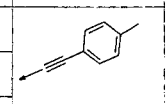
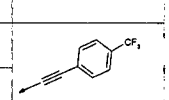
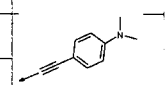
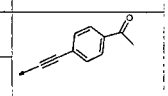
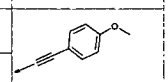
N.°	Racémico o enantiómero	R3 
1081	rac	
1082	+	
1083	-	
1084	rac	
1085	+	
1086	-	
1087	rac	
1088	+	
1089	-	
1090	rac	
1091	+	
1092	-	
1093	rac	
1094	+	
1095	-	
1096	rac	
1097	+	
1098	-	
1099	rac	
1100	+	

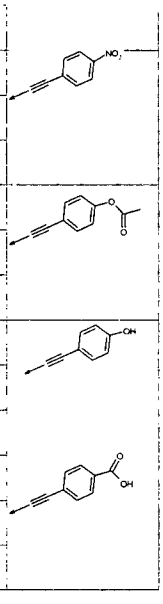
1101	–	
1102	rac	
1103	+	
1104	–	
1105	rac	
1106	+	
1107	–	
1108	rac	
1109	+	
1110	–	
1111	rac	
1112	+	
1113	–	
1114	rac	
1115	+	
1116	–	
1117	rac	
1118	+	
1119	–	
1120	rac	
1121	+	
1122	–	
1123	rac	
1124	+	
1125	–	
1126	rac	
1127	+	
1128	–	
1129	rac	
1130	+	

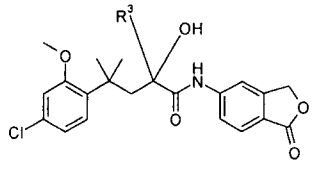
1131	-	
1132	rac	
1133	+	
1134	-	
1135	rac	
1136	+	
1137	-	
1138	rac	
1139	+	
1140	-	

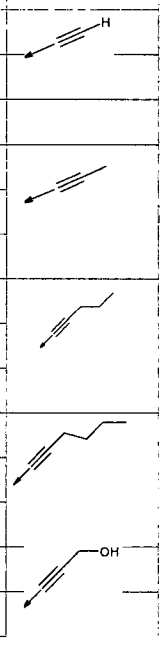


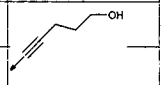
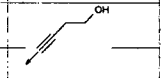
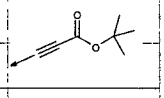
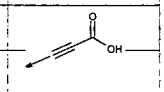
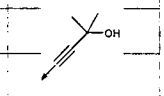
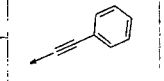
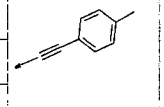
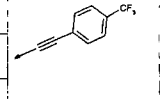
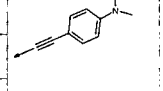
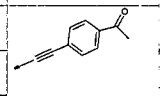
N.°	Racémico o enantiómero	R3
1141	rac	
1142	+	
1143	-	
1144	rac	
1145	+	
1146	-	
1147	rac	
1148	+	
1149	-	
1150	rac	
1151	+	
1152	-	
1153	rac	
1154	+	
1155	-	
1156	rac	
1157	+	

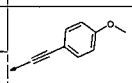
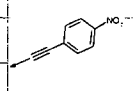
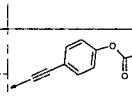
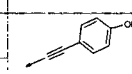
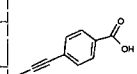
1158	-	
1159	rac	
1160	+	
1161	-	
1162	rac	
1163	+	
1164	-	
1165	rac	
1166	+	
1167	-	
1168	rac	
1169	+	
1170	-	
1171	rac	
1172	+	
1173	-	
1174	rac	
1175	+	
1176	-	
1177	rac	
1178	+	
1179	-	
1180	rac	
1181	+	
1182	-	
1183	rac	
1184	+	
1185	-	
1186	rac	
1187	+	

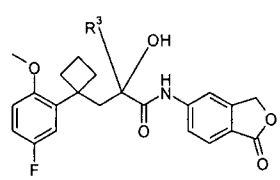
1188	–	
1189	rac	
1190	+	
1191	–	
1192	rac	
1193	+	
1194	–	
1195	rac	
1196	+	
1197	–	
1198	rac	
1199	+	
1200	–	

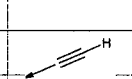
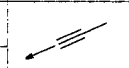


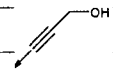
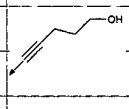
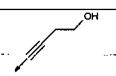
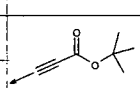
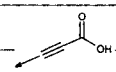
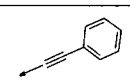
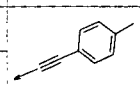
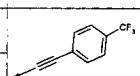
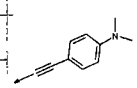
N.°	Racémico o enantiómero	R3
1201	rac	
1202	+	
1203	–	
1204	rac	
1205	+	
1206	–	
1207	rac	
1208	+	
1209	–	
1210	rac	
1211	+	
1212	–	
1213	rac	
1214	+	

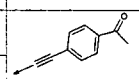
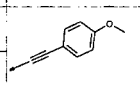
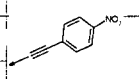
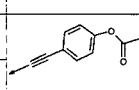
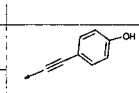
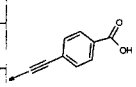
1215	–	
1216	rac	
1217	+	
1218	–	
1219	rac	
1220	+	
1221	–	
1222	rac	
1223	+	
1224	–	
1225	rac	
1226	+	
1227	–	
1228	rac	
1229	+	
1230	–	
1231	rac	
1232	+	
1233	–	
1234	rac	
1235	+	
1236	–	
1237	rac	
1238	+	
1239	–	
1240	rac	
1241	+	
1242	–	
1243	rac	
1244	+	

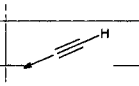
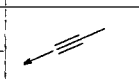
1245	-	
1246	rac	
1247	+	
1248	-	
1249	rac	
1250	+	
1251	-	
1252	rac	
1253	+	
1254	-	
1255	rac	
1256	+	
1257	-	
1258	rac	
1259	+	
1260	-	

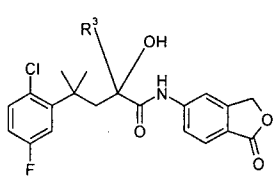


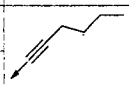
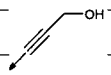
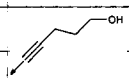
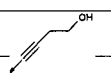
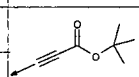
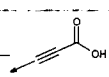
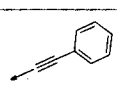
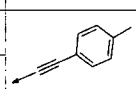
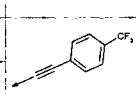
N.°	Racémico o enantiómero	R3
1261	rac	
1262	+	
1263	-	
1264	rac	
1265	+	
1266	-	
1267	rac	
1268	+	
1269	-	
1270	rac	
1271	+	

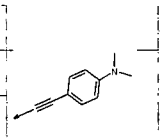
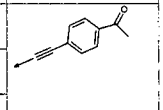
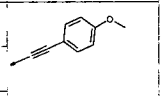
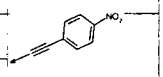
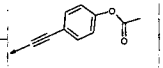
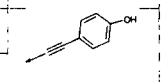
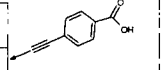
1272	–	
1273	rac	
1274	+	
1275	–	
1276	rac	
1277	+	
1278	–	
1279	rac	
1280	+	
1281	–	
1282	rac	
1283	+	
1284	–	
1285	rac	
1286	+	
1287	–	
1288	rac	
1289	+	
1290	–	
1291	rac	
1292	+	
1293	–	
1294	rac	
1295	+	
1296	–	
1297	rac	
1298	+	
1299	–	
1300	rac	
1301	+	

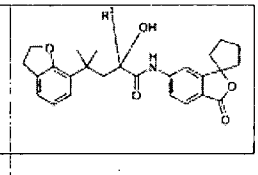
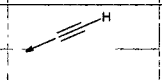
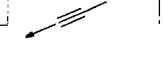
1302	-	
1303	rac	
1304	+	
1305	-	
1306	rac	
1307	+	
1308	-	
1309	rac	
1310	+	
1311	-	
1312	rac	
1313	+	
1314	-	
1315	rac	
1316	+	
1317	-	
1318	rac	
1319	+	
1320	-	

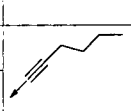
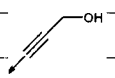
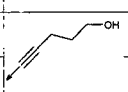
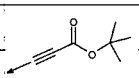
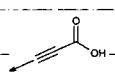
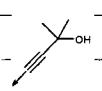
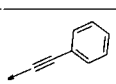
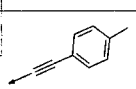
N.°	Racémico o enantiómero	R3
1321	rac	
1322	+	
1323	-	
1324	rac	
1325	+	
1326	-	
1327	rac	
1328	+	

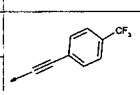
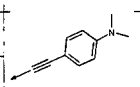
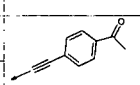
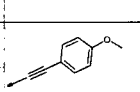
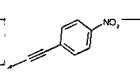
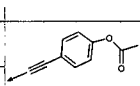
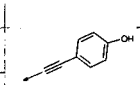
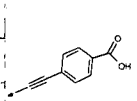


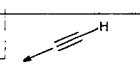
1329	-	
1330	rac	
1331	+	
1332	-	
1333	rac	
1334	+	
1335	-	
1336	rac	
1337	+	
1338	-	
1339	rac	
1340	+	
1341	-	
1342	rac	
1343	+	
1344	-	
1345	rac	
1346	+	
1347	-	
1348	rac	
1349	+	
1350	-	
1351	rac	
1352	+	
1353	-	
1354	rac	
1355	+	
1356	-	
1357	rac	
1358	+	

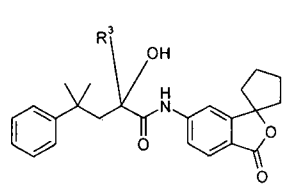
1359	-	
1360	rac	
1361	+	
1362	-	
1363	rac	
1364	+	
1365	-	
1366	rac	
1367	+	
1368	-	
1369	rac	
1370	+	
1371	-	
1372	rac	
1373	+	
1374	-	
1375	rac	
1376	+	
1377	-	
1378	rac	
1379	+	
1380	-	

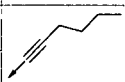
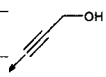
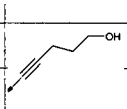
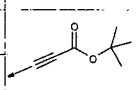
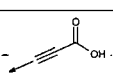
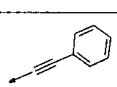
N.°	Racémico o enantiómero	R3	
1381	rac		
1382	+		
1383	-		
1384	rac		

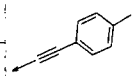
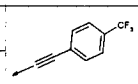
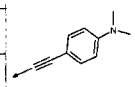
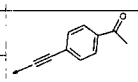
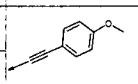
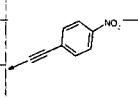
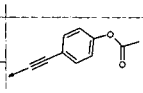
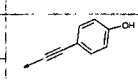
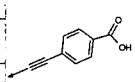
1385	+	
1386	-	
1387	rac	
1388	+	
1389	-	
1390	rac	
1391	+	
1392	-	
1393	rac	
1394	+	
1395	-	
1396	rac	
1397	+	
1398	-	
1399	rac	
1400	+	
1401	-	
1402	rac	
1403	+	
1404	-	
1405	rac	
1406	+	
1407	-	
1408	rac	
1409	+	
1410	-	
1411	rac	
1412	+	
1413	-	
1414	rac	

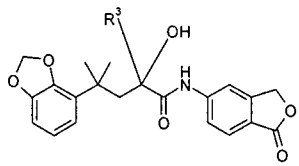
1415	+	
1416	-	
1417	rac	
1418	+	
1419	-	
1420	rac	
1421	+	
1422	-	
1423	rac	
1424	+	
1425	-	
1426	rac	
1427	+	
1428	-	
1429	rac	
1430	+	
1431	-	
1432	rac	
1433	+	
1434	-	
1435	rac	
1436	+	
1437	-	
1438	rac	
1439	+	
1440	-	

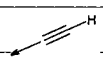
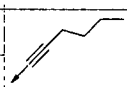
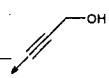
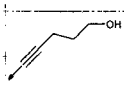
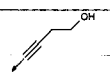
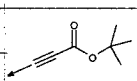
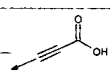
N.°	Racémico o enantiómero	R3
1441	rac	

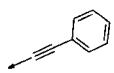
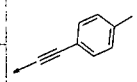
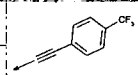
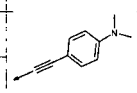
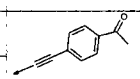
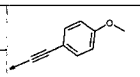
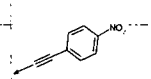
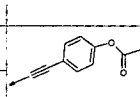
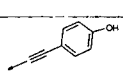


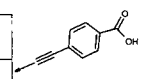
1442	+	
1443	–	
1444	rac	
1445	+	
1446	–	
1447	rac	
1448	+	
1449	–	
1450	rac	
1451	+	
1452	–	
1453	rac	
1454	+	
1455	–	
1456	rac	
1457	+	
1458	–	
1459	rac	
1460	+	
1461	–	
1462	rac	
1463	+	
1464	–	
1465	rac	
1466	+	
1467	–	
1468	rac	
1469	+	
1470	–	
1471	rac	

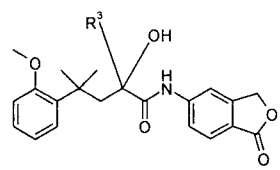
1472	+	
1473	–	
1474	rac	
1475	+	
1476	–	
1477	rac	
1478	+	
1479	–	
1480	rac	
1481	+	
1482	–	
1483	rac	
1484	+	
1485	–	
1486	rac	
1487	+	
1488	–	
1489	rac	
1490	+	
1491	–	
1492	rac	
1493	+	
1494	–	
1495	rac	
1496	+	
1497	–	
1498	rac	
1499	+	
1500	–	

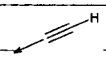
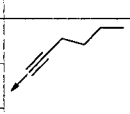
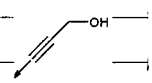
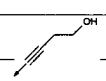
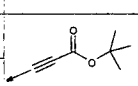


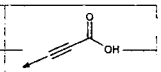
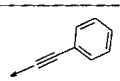
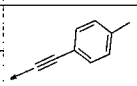
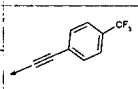
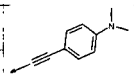
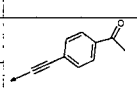
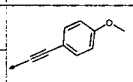
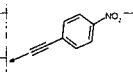
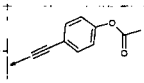
N.º	Racémico o enantiómero	R3
1501	rac	
1502	+	
1503	-	
1504	rac	
1505	+	
1506	-	
1507	rac	
1508	+	
1509	-	
1510	rac	
1511	+	
1512	-	
1513	rac	
1514	+	
1515	-	
1516	rac	
1517	+	
1518	-	
1519	rac	
1520	+	
1521	-	
1522	rac	
1523	+	
1524	-	
1525	rac	
1526	+	
1527	-	
1528	rac	

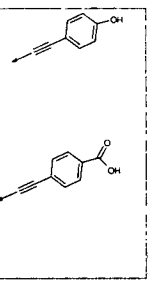
1529	+	
1530	–	
1531	rac	
1532	+	
1533	–	
1534	rac	
1535	+	
1536	–	
1537	rac	
1538	+	
1539	–	
1540	rac	
1541	+	
1542	–	
1543	rac	
1544	+	
1545	–	
1546	rac	
1547	+	
1548	–	
1549	rac	
1550	+	
1551	–	
1552	rac	
1553	+	
1554	–	
1555	rac	
1556	+	
1557	–	

1558	rac	
1559	+	
1560	–	



N.°	Racémico o enantiómero	R3
1561	rac	
1562	+	
1563	–	
1564	rac	
1565	+	
1566	–	
1567	rac	
1568	+	
1569	–	
1570	rac	
1571	+	
1572	–	
1573	rac	
1574	+	
1575	–	
1576	rac	
1577	+	
1578	–	
1579	rac	
1580	+	
1581	–	
1582	rac	
1583	+	
1584	–	

1585	rac	
1586	+	
1587	–	
1588	rac	
1589	+	
1590	–	
1591	rac	
1592	+	
1593	–	
1594	rac	
1595	+	
1596	–	
1597	rac	
1598	+	
1599	–	
1600	rac	
1601	+	
1602	–	
1603	rac	
1604	+	
1605	–	
1606	rac	
1607	+	
1608	–	
1609	rac	
1610	+	
1611	–	
1612	rac	
1613	+	
1614	–	

1615	rac	
1616	+	
1617	-	
1618	rac	
1619	+	
1620	-	

Caracterización biológica de los compuestos según la invención

La identificación de moduladores de receptores de la progesterona se puede llevar a cabo con ayuda de métodos sencillos, programas de prueba conocidos por el especialista. Para ello se puede incubar, a modo de ejemplo, un compuesto que se desea ensayar junto con un gestágeno en un sistema de pruebas para receptores de la progesterona y verificar si en este sistema de pruebas se altera la acción mediada por la progesterona en presencia del modulador.

Las sustancias de la fórmula general I según la invención se ensayaron en los siguientes modelos:

Prueba de unión del receptor de progesterona

Medición de la afinidad de unión del receptor:

La afinidad de unión del receptor se determinó por unión competitiva de una hormona marcada con ^{3}H de unión específica (trazador) y el compuesto por ensayar en receptores en el citosol de órganos de animales blanco. En este caso se pretendían saturación del receptor y equilibrio de la reacción.

Los trazadores y las concentraciones crecientes del compuesto por ensayar (competidor) se coincubaron a 0-4 °C durante 18 h con la fracción de citosol que contenía el receptor. Después de separar el trazador no unido con una suspensión de carbón-dextrano, se midió para cada concentración la proporción de trazador unido al receptor y a partir de la serie de concentraciones se determinó la IC_{50}. Como cociente de los valores de IC_{50} de la sustancia de referencia y el compuesto por ensayar (x 100%) se calculó la afinidad de unión molar relativa (RBA) (RBA de la sustancia de referencia = 100%).

Para los tipos de receptores se seleccionaron las siguientes condiciones de incubación:

Receptor de progesterona:

Citosol de útero de conejo cebado con estradiol, homogeneizado en tampón de TED (20 mMtris/HCl, pH 7,4; 1 mM de tetraacetato de etilendiamina, 2 mM de ditiotreitol) con 250 mM de sacarosa; conservado a -30 °C. Trazador: ^{3}H-ORG 2058, 5 nM; sustancia de referencia: progesterona.

Receptor de glucocorticoides:

Citosol de timo de la rata adrenalectomizada, timos conservados a -30 °C; tampón: TED. Trazador: ^{3}H-dexametasona, 20 nM; sustancia de referencia: dexametasona.

Las afinidades relativas de unión con el receptor (valores de RBA) de los compuestos de la fórmula general (I)

según la invención en el receptor de progesterona son de entre el 3 y el 100% respecto de la progesterona. En el receptor de glucocorticoides, los valores de RBA están en el rango del 3 al 30% respecto de la dexametasona.

Conforme a ello, los compuestos según la invención tienen una gran afinidad por el receptor de progesterona, pero sólo una escasa afinidad por el receptor de glucocorticoides.

Antagonismo en el receptor de progesterona PR-B

El ensayo de transactivación se realiza tal como se describió en el documento WO 02/054064.

Agonismo en el receptor de progesterona PR-B

El ensayo de transactivación se realiza tal como se describió en Fuhrmann et al. (Fuhrmann U., Hess-Stump H., Cleve A., Neef G., Schwede W., Hoffmann J., Fritzemeier K.-H., Chwalisz K., Journal of Medicinal Chem, 43, 26, 2000, 5010-5016).

Ejemplo	Acción antagonista		Acción agonista	
	IC_{50} [nM]	Eficacia [%]	EC_{50} [nM]	Eficacia [%]
9	3	96	n. b.	3
13	3	92	n. b.	7
3b	0,4	97	n. b.	2
7	4	82	2	11

Dosis

Para el uso según la invención, los moduladores de los receptores de progesterona se pueden administrar por vía oral, enteral, parenteral o transdérmica.

En general, se han de esperar resultados satisfactorios en el tratamiento de las indicaciones mencionadas más arriba cuando las dosis diarias comprenden un rango de 1 µg a 500 mg del compuesto según la invención.

Las dosis apropiadas de los compuestos según la invención en el ser humano para el tratamiento de endometriosis, de leiomiomas de útero y hemorragias disfuncionales, así como para el uso en el control de la fertilidad y la terapia de reemplazo hormonal, son de 50 µg a 500 mg por día, según la edad y la constitución del paciente, pudiendo aplicar la dosis diaria necesaria por administración única o múltiple.

Para el tratamiento de carcinomas de mama, el rango posológico para los compuestos según la invención comprende 10 mg a 1000 mg diarios.

La formulación de los preparados farmacéuticos en base a los nuevos compuestos se realiza de un modo en que es conocidos por los técnicos, elaborando el principio activo con sustancias de soporte, rellenos, agentes que influyen sobre la desintegración, aglutinantes, conservadores de la humedad, lubricantes, agentes absorbentes, diluyentes, correctores del sabor, colorantes, etc. usuales en galénica y convirtiéndolos en la forma de aplicación deseada. En este ca-

so, se hace referencia a Remington´s Pharmaceutical Science, 15th ed. Mack Publishing Company, East Pennsylvania (1980).

Para la aplicación oral se tienen en cuenta, en especial, comprimidos, comprimidos recubiertos, grageas, cápsulas, píldoras, polvos, granulados, pastillas, suspensiones, emulsiones o soluciones.

Para la aplicación parenteral son posibles las preparaciones inyectables y las infusiones.

Para la inyección intraarticular se pueden usar suspensiones cristalinas preparadas de forma correspondiente.

Para la inyección intramuscular se pueden utilizar soluciones o suspensiones acuosas y oleosas para inyección y las correspondientes preparaciones de depósito.

Para la aplicación rectal, se pueden usar los nuevos compuestos en forma de supositorios, cápsulas, soluciones (por ejemplo, en forma de enemas) y ungüentos tanto para la terapia sistémica como también local.

También se pueden mencionar como preparado fármacos para la aplicación vaginal.

Para la aplicación pulmonar, se pueden usar los nuevos compuestos en forma de aerosoles e inhalados.

Para la aplicación transdérmica son posibles emplastos o bien, para la aplicación tópica, formulaciones en geles, ungüentos, ungüentos grasos, cremas, pastas, polvos, leche y tinturas. La dosis de los compuestos de la fórmula general I

deberá ser en estas preparaciones del 0,01% - 20%, a fin de lograr una suficiente acción farmacológica.

Los comprimidos correspondientes se pueden obtener, por ejemplo, por mezcladura del principio activo con conocidos excipientes, por ejemplo, diluyentes inertes tales como dextrosa, azúcar, sorbita, manita, polivinilpirrolidona, desintegrantes tales como almidón de maíz o ácido algínico, aglutinantes tales como almidón o gelatina, desintegrantes tales como estearato de magnesio o talco y/o agentes para lograr un efecto de depósito tales como carboxipolimetileno, carboximetilcelulosa, acetato-ftalato de celulosa o acetato de polivinilo. Los comprimidos también pueden estar compuestos de varias capas.

Conforme con ello, se pueden preparar grageas por recubrimiento de núcleos preparados análogamente a los comprimidos, con agentes utilizados usualmente en cubiertas de grageas, por ejemplo, polivinilpirrolidona o goma laca, goma arábiga, talco, óxido de titanio o azúcar. En este caso, la cubierta de la gragea también puede estar compuesta de varias capas, pudiendo usar los excipientes mencionados en el caso de los comprimidos.

Las soluciones o suspensiones de los compuestos de la fórmula general I según la invención pueden contener adicionalmente agentes correctores del sabor tales como sacarina, ciclamato o azúcar, así como, por ejemplo, sustancias aromá-

ticas tales como vainillina o extracto de naranja. Además pueden contener agentes auxiliares de suspensión tales como carboximetilcelulosa sódica o conservantes tal como p-hidroxibenzoato.

Las cápsulas que contienen los compuestos de la fórmula general I pueden prepararse, por ejemplo, mezclando el o los compuestos de la fórmula general I con un portador inerte como lactosa o sorbita y encapsulándolos en cápsulas de gelatina.

Los supositorios apropiados se pueden preparar, por ejemplo, por mezcladura con agentes de soporte previstos para ese fin tales como grasas neutras o polietilenglicol o bien sus derivados.

Los compuestos según la invención de la fórmula general (I) o sus sales farmacéuticamente aceptables pueden utilizarse, en virtud de su eficacia antagonista o parcialmente agonista, para la preparación de un medicamento, en especial para el tratamiento y la prevención de enfermedades ginecológicas tales como endometriosis, leiomiomas de útero, hemorragias disfuncionales y dismenorrea. Además, se pueden usar contra irregularidades hormonales, para provocar la menstruación y solos o en combinación con prostaglandinas y/u oxitocina para inducir el parto.

Los compuestos según la invención de la fórmula general (I) o sus sales farmacéuticamente aceptables también son

apropiados para la elaboración de preparados para la anticoncepción en la mujer (ver también los documentos WO 93/23020, WO 93/21927).

Los compuestos según la invención o sus sales farmacéuticamente aceptables también se pueden emplear, solos o en combinación, con un modulador selectivo de receptor de estrógeno (SERM) para la terapia de reemplazo hormonal femenina.

Por otra parte, los compuestos mencionados ejercen un efecto antiproliferativo en tumores dependientes de hormonas. Por ello, son apropiados para la terapia de carcinomas dependientes de hormonas tales como, por ejemplo, carcinoma de mama, próstata y endometrio.

Los compuestos según la invención o sus sales farmacéuticamente aceptables pueden utilizarse para el tratamiento de carcinomas dependientes de hormonas tanto en la terapia de primera línea como en la terapia de segunda línea, en especial después del fracaso terapéutico de tamoxifeno.

Los compuestos de la fórmula general (I) según la invención, de eficacia antagonista o parcialmente agonista, o sus sales farmacéuticamente aceptables también se pueden utilizar en combinación con compuestos de eficacia antiestrogénica (antagonistas del receptor de estrógeno o inhibidores de aromatasa) o moduladores selectivos de receptor de estrógeno (SERM) para la elaboración de preparados farmacéu-

ticos para el tratamiento de tumores dependientes de hormonas. Para el tratamiento de endometriosis o leiomiomas de útero, los compuestos según la invención también se pueden utilizar en combinación con SERM o un antiestrógeno (antagonistas del receptor de estrógeno o inhibidores de aromatasa). En el tratamiento de tumores dependientes de hormonas, pueden estar previstos el modulador del receptor de progesterona y el antiestrógeno (antagonistas del receptor de estrógeno o inhibidores de aromatasa) o el SERM para una administración simultánea o también secuencial. En la administración secuencial, primero se administra preferentemente el antiestrógeno (antagonista del receptor de estrógeno o inhibidor de aromatasa) o SERM y luego el modulador del receptor de progesterona.

En este caso, para la combinación con los moduladores no esteroides de receptor de progesterona según la invención, se tienen en cuenta, por ejemplo, los siguientes antiestrógenos (antagonistas del receptor de estrógeno o inhibidores de aromatasa) o bien SERM:

tamoxifeno, 5-(4-{5-[(RS)-(4,4,5,5,5-pentafluoropentil)sulfinil]pentiloxi}fenil)-6-fenil-8,9-dihidro-7H-benzociclohepten-2-ol (documento WO 00/03979), ICI 182 780 (7alfa-[9-(4,4,5,5-pentafluoropentilsulfinil)nonil]estra-1,3,5(10)-trien-3,17-beta-diol), 11beta-fluoro-7alfa-[5-(metil{3-[(4,4,5,5,5-

330

pentafluoropentil)sulfanil]propil}amino)pentil]estra-1,3,5(10)-trien-3,17beta-diol (WO 98/07740), 11beta-fluoro-7alfa-{5-[metil(7,7,8,8,9,9,10,10,10-nonafluorodecil)amino]pentil}estra-1,3,5(10)-trien-3,17beta-diol (documento WO 99/33855), 11beta-fluoro-17alfa-metil-7alfa-{5-[metil8,8,9,9,9-pentafluorononil)amino]pentil}estra-1,3,5(10)-trien-3,17beta-diol (WO 03/045972), clomifeno, raloxifeno, así como otros compuestos de eficacia antiestrogénica, e inhibidores de la aromatasa tales como, p. ej., fadrozol, formestano, letrozol, anastrozol o atamestano.

Finalmente, la presente invención se refiere también al uso de compuestos de la fórmula general I, opcionalmente junto con un antiestrógeno o SERM, para la preparación de un agente farmacéutico.

Además, la presente invención se refiere a composiciones farmacéuticas que contienen al menos un compuesto según la invención, opcionalmente en forma de una sal aceptable para uso farmacéutico / farmacológica, sin o junto con excipientes y/o coadyuvantes aceptable para uso farmacéutico.

Estas composiciones farmacéuticas y medicamentos pueden estar previstos para la aplicación oral, rectal, vaginal, subcutánea, percutánea, intravenosa o intramuscular. Contienen, junto a los vehículos y/o diluyentes usuales, al menos un compuesto según la invención.

Los medicamentos de la invención se preparan con los vehículos o diluyentes sólidos o líquidos usuales y los excipientes farmacéutico-técnicos usualmente utilizados según el tipo de aplicación deseado con una dosis apropiada de forma conocida. Las preparaciones preferidas consisten en una forma de administración que es apropiada para la aplicación oral. Las formas de administración de este tipo son, por ejemplo, comprimidos, comprimidos recubiertos, grageas, cápsulas, píldoras, polvos, soluciones o suspensiones o también formas de depósito.

Las composiciones farmacéuticas que contienen al menos uno de los compuestos según la invención se aplican preferentemente por vía oral.

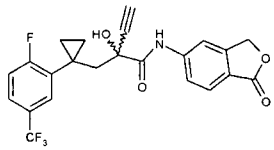
Se tienen en cuenta también las preparaciones parenterales como las soluciones inyectables.

Además, se mencionan como preparaciones, por ejemplo, supositorios y fármacos para la aplicación vaginal.

Los ejemplos siguientes sirven para explicar con mayor detalle el objeto de la invención, sin pretender restringirla a ellos.

La preparación del compuesto de partida 5-{3-[1-(2-fluoro-5-trifluorometilfenil)-ciclopropil]-2-oxopropionilamino}ftalida se describe en la patente WO 200375915 y la preparación de 5-{3-[1-fenil-ciclopropil]-2-oxopropionilamino}ftalida, en el documento WO 9854159.

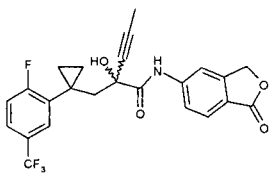
Rac-5-{2-etinil-2-hidroxi-3-[1-(2-fluoro-5-trifluorometilfenil)-ciclopropil]-propionilamino}ftalida 1



Se adicionó bromuro de etinilmagnesio (6 ml, 0,5 M en tetrahidrofurano) a una solución helada de 5-{3-[1-(2-fluoro-5-trifluorometilfenil)-ciclopropil]-2-oxopropionilamino}ftalida (632 mg) en THF (4 ml). Se dejó llegar a la solución de reacción a temperatura ambiente bajo argón en un lapso de 3 h. Luego se vertió la mezcla de reacción en una solución saturada helada de cloruro de amonio. Se extrajo con acetato de etilo. Las fases orgánicas combinadas se lavaron con solución saturada de cloruro de sodio y se secaron sobre sulfato de sodio. El producto crudo obtenido se cromatografió en gel de sílice. Se obtuvieron 2,2 g de producto.

^{1}H-RMN (ppm, $CDCl_3$, 400 MHz): 0,83 (1H), 0,92-1,10 (2H), 2,37 (1H), 2,56 (1H), 2,59 (1H), 3,10 (1H), 5,28 (2H), 7,02 (1H), 7,31 (1H), 7,37 (1H), 7,58 (1H), 7,86 (1H), 7,94 (1H), 8,70 (1H).

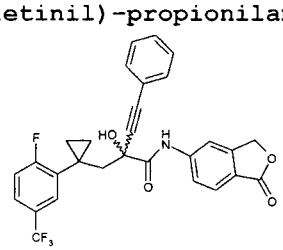
Rac-5-{2-hidroxi-3-[1-(2-fluoro-5-trifluorometilfenil)-ciclopropil]-2-propinil-propionilamino}ftalida 2



De modo análogo al Ejemplo 1 se obtuvieron a partir de bromuro de 1-propinilmagnesio (2 ml de solución 0,5 M en tetrahidrofurano) y 210 mg de 6-[4-(2-cloro-4-fluorofenil)-4-metil-2-oxovaleroilamino]-4-metil-2,3-benzoxazin-1-ona, 145 mg de producto.

^{1}H-RMN (ppm, $CDCl_3$, 400 MHz): 0,86 (1H), 0,90-1,05 (3H), 1,72 (3H), 2,35 (1H), 2,49 (1H), 2,96 (1H), 5,27 (2H), 7,03 (1H), 7,30 (1H), 7,36 (1H), 7,58 (1H), 7,85 (1H), 7,98 (1H9, 8,73 (1H).

(+)-5-{2-Hidroxi-3-[1-(2-fluoro-5-trifluorometilfenil)-ciclopropil]-2-fenil-propionilamino}ftalida 3a y (-)-5-{2-hidroxi-3-[1-(2-fluoro-5-trifluorometilfenil)-ciclopropil]-2-(feniletinil)-propionilamino}ftalida 3b



A una solución de 110 µl de fenilacetileno en tetrahidrofurano se añadió a -78 °C n-butil-litio (625 µl, 1,6 M en hexano). Se dejó agitar durante 30 minutos a esta temperatura y luego se vertió gota a gota una solución de 5-{3-[1-(2-

fluoro-5-trifluorometilfenil)-ciclopropil]-2-oxopropionilamino}ftalida (210 mg) en 5 ml de tetrahidrofurano. A continuación se dejó llevar la temperatura a 23 °C durante aproximadamente 3 h y luego se agitó durante 10 h. Después se vertió la mezcla de reacción en solución saturada helada de cloruro de amonio. Se extrajo con acetato de etilo. Las fases orgánicas combinadas se lavaron con solución saturada de cloruro de sodio y se secaron sobre sulfato de sodio. El producto crudo se cromatografió en gel de sílice. La mezcla racémica obtenida se separó luego por HPLC quiral preparativa (columna Chiralpak AD 250 x 10 mm) en los enantiómeros 3a (46 mg) y 3b (47 mg).

3a y **3b**:

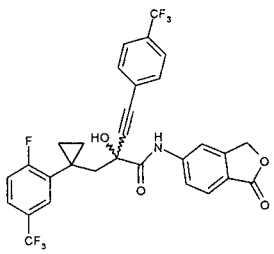
^{1}H-RMN (ppm, $CDCl_3$, 300 MHz): 0,88 (1H), 0,95-1,11 (3H), 2,46 (1H), 2,65 (1H), 3,10 (1H), 5,27 (2H), 7,00 (1H), 7,24-7,42 (7H), 7,61 (1H), 7,84 (1H), 7,98 (1H), 8,80 (1H).

3a : $[\alpha]^D_{20}$: + 12,9° ($CHCl_3$, 1,06 g/100 ml; λ = 589 nM)

3b : $[\alpha]^D_{20}$: - 14,4° ($CHCl_3$, 1,03 g/100 ml; λ = 589 nM)

De modo análogo al Ejemplo 3 se prepararon a partir de 5-{3-[1-(2-fluoro-5-trifluorometilfenil)-ciclopropil]-2-oxopropionilamino}ftalida y el correspondiente arilacetiluro de litio los compuestos 4 y 5:

Rac-5-{2-hidroxi-3-[1-(2-fluoro-5-trifluorometilfenil)-ciclopropil]-2-[(4-trifluorometilfenil)etinil]propionilamino}ftalida 4



^{1}H-RMN (ppm, $CDCl_3$, 300 MHz): 0,92 (1H), 0,99-1,16 (3H), 2,55 (1H), 2,68 (1H), 3,27 (1H), 5,30 (2H), 7,03 (1H), 7,30-7,52 (4H), 7,55-7,62 (2H), 6,67 (1H), 7,99 (1H), 8,03 (1H), 8,84 (1H).

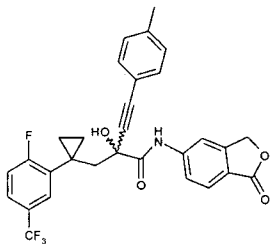
(+)-5-{2-Hidroxi-3-[1-(2-fluoro-5-trifluorometilfenil)-ciclopropil]-2-[(4-trifluorometilfenil)etinil]propionilamino}ftalida 4a y (-)-5-{2-hidroxi-3-[1-(2-fluoro-5-trifluorometilfenil)-ciclopropil]-2-[(4-trifluorometilfenil)etinil]propionilamino}ftalida 4b

La mezcla racémica descrita en el punto 4 (150 mg) se separó por HPLC quiral preparativa (columna Chiralpak AD 250 x 10 mm) en los enantiómeros 4a (51 mg) y 4b (62 mg).

4a : $[\alpha]^D_{20}$: + 6,3° ($CHCl_3$, 1,07 g/100 ml; λ=589 nM)

4b : $[\alpha]^D_{20}$: - 5,3° ($CHCl_3$, 1,09 g/100 ml; λ=589 nM)

rac-5-{2-Hidroxi-3-[1-(2-fluoro-5-trifluorometilfenil)-ciclopropil]-2-[(4-metilfenil)etinil]propionilamino}ftalida 5



^{1}H-RMN (ppm, $CDCl_3$, 300 MHz): 0,87 (1H), 0,93-1,15 (3H), 2,38 (3H), 2,45 (1H), 2,66 (1H), 3,11 (1H), 5,25 (2H), 6,99 (1H), 7,10 (2H), 7,18-7,38 (4H), 7,61 (1H), 7,86 (1H), 8,00 (1H), 8,80 (1H).

(+)-5-{2-Hidroxi-3-[1-(2-fluoro-5-trifluorometilfenil)-ciclopropil]-2-[(4-metilfenil)etinil]propionilamino}ftalida 5a y

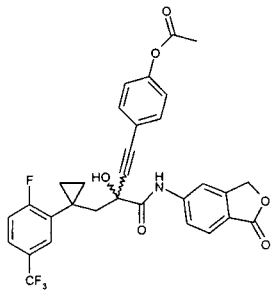
(-)-5-{2-hidroxi-3-[1-(2-fluoro-5-trifluorometilfenil)-ciclopropil]-2-[(4-metilfenil)etinil]propionilamino}ftalida 5b

La mezcla racémica descrita en el punto 5 (109 mg) se separó por HPLC quiral preparativa (columna Chiralpak AD 250 x 10 mm) en los enantiómeros 5a (41 mg) y 5b (28 mg).

5a : $[\alpha]^{D}_{20}$: + 14,8° ($CHCl_3$, 1,07 g/100 ml; λ=589 nM)

5b : $[\alpha]^{D}_{20}$: - 16,3° ($CHCl_3$, 1,13 g/100 ml; λ=589 nM)

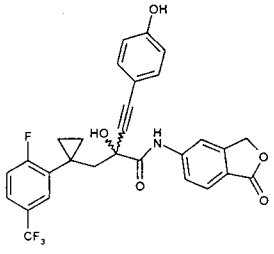
rac-5-{2-[(4-Acetoxifenil)etinil]-2-hidroxi-3-[1-(2-fluoro-5-trifluorometilfenil)-ciclopropil]-propionilamino}ftalida 6



Se hizo reaccionar una suspensión del compuesto descrito en el Ejemplo 1 (104 mg), trifenilfosfina (12,2 mg) y yoduro de cobre (8,9 mg), acetato de 4-yodofenilo (92 mg), acetato de paladio (5,3 mg) en THF (5 ml) y trietilamina (5 ml) durante 1 h en baño de ultrasonido a 25 °C bajo argón. Luego se vertió en solución saturada acuosa de cloruro de amonio. Se extrajo con acetato de etilo, se lavó con agua y solución saturada de cloruro de sodio. Las fases orgánicas combinadas se secaron sobre sulfato de sodio. Después de la cromatografía en columna del producto crudo en gel de sílice se obtuvieron 55 mg de producto.

^{1}H-RMN (ppm, $CDCl_3$, 400 MHz): 0,88 (1H), 0,95-1,10 (3H), 2,29 (3H), 2,45 (1H), 2,63 (1H), 3,17 (1H), 5,29 (2H), 6,97-7,07 (3H), 7,28-7,37 (4H), 7,60 (1H), 7,84 (1H), 7,98 (1H), 8,80 (1H).

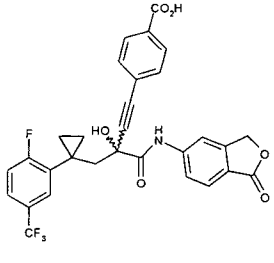
rac-5-{2-Hidroxi-2-[(4-hidroxifenil)etinil]-3-[1-(2-fluoro-5-trifluorometilfenil)-ciclopropil]-propionilamino}ftalida 7



Una solución del compuesto descrito en el punto 6 (45 mg) en 5 ml de metanol se mezcló con hidrógeno-carbonato de sodio (130 mg). Se agitó durante 2 horas a 23 °C. Luego se diluyó la mezcla de reacción con acetato de etilo. A continuación se lavó dos veces con solución saturada de cloruro de sodio. Después de secar sobre sulfato de sodio, se purificó el producto crudo por cromatografía en columna de gel de sílice. Se obtuvieron 38 mg de producto.

^{1}H-RMN (ppm, $CDCl_3$, 300 MHz): 0,87 (1H), 0,92-1,11 (3H), 2,43 (1H), 2,64 (1H), 3,11 (1H), 5,27 (2H), 5,67 (1H), 6,73 (2H), 6,98 (1H), 7,14 (2H), 7,28-7,38 (2H), 7,60 (1H), 7,85 (1H), 7,97 (1H), 8,84 (1H).

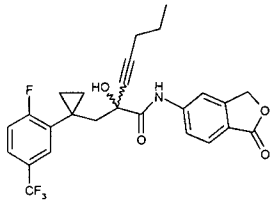
rac-5-{2-[(4-Carboxifenil)etinil]-2-hidroxi-3-[1-(2-fluoro-5-trifluorometilfenil)-ciclopropil]-propionilamino}ftalida 8



De modo análogo al Ejemplo 6 se preparó a partir del compuesto descrito en el Ejemplo 1 y ácido 4-yodobenzoico el compuesto 8.

^{1}H-RMN (ppm, $CDCl_3$/MeOD (5%), 400 MHz): 0,82 (1H), 0,89-1,05 (3H), 2,37 (1H), 2,65 (1H), 5,24 (2H), 6,97 (1H), 7,35 (1H), 7,44 (2H), 7,50-7,65 (2H), 7,72 (1H), 7,80 (1H), 7,92 (2H).

rac-5-{2-Hidroxi-3-[1-(2-fluoro-5-trifluorometilfenil)-ciclopropil]-2-(pentin-1-il)-propionilamino}ftalida 9



Una solución de 1-pentina (0,94 ml) en THF (9 ml) se mezcló a -78 °C con n-BuLi (0,6 ml, 1,6 M en hexano). Se dejó bajo agitación durante 30 min a -78 °C y luego se añadió una solución de 5-{3-[1-(2-fluoro-5-trifluorometilfenil)-ciclopropil]-2-oxopropionilamino}ftalida (200 mg) en 3 ml de tetrahidrofurano. Luego se dejó llegar a una temperatura de 23 °C durante aproximadamente 3 horas y se agitó durante 10 h a esta temperatura. Después se vertió la mezcla de reacción en solución saturada helada de cloruro de amonio. Se extrajo con acetato de etilo. Las fases orgánicas combinadas se lavaron con solución saturada de cloruro de sodio y se

secaron sobre sulfato de sodio. El producto crudo se cromatografió en gel de sílice. Se obtuvieron 130 mg de producto.

^{1}H-RMN (ppm, $CDCl_3$, 400 MHz): 0,82 (1H), 0,92-1,07 (6H), 1,45 (2H), 2,08 (2H), 2,30 (1H), 2,53 (1H), 2,83 (1H), 5,27 (2H), 7,02 (1H), 7,29 (1H), 7,36 (1H), 7,57 (1H), 7,84 (1H), 7,96 (1H), 8,72 (1H).

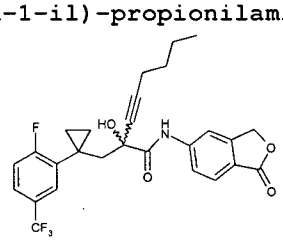
(+)-5-{2-Hidroxi-3-[1-(2-fluoro-5-trifluorometilfenil)-ciclopropil]-2-(pentin-1-il)-propionilamino}ftalida 9a y (-)-5-{2-hidroxi-3-[1-(2-fluoro-5-trifluorometilfenil)-ciclopropil]-2-(pentin-1-il)-propionilamino}ftalida 9b

La mezcla racémica descrita en el punto 9 (120 mg) se separó por HPLC quiral preparativa (columna Chiralpak AD 250 x 10 mm) en los enantiómeros 9a (46 mg) y 9b (47 mg).

9a : $[\alpha]^D_{20}$: + 10,9° ($CHCl_3$, 1,01 g/100 ml; λ=589 nM)

9b : $[\alpha]^D_{20}$: - 10,6° ($CHCl_3$, 1,08 g/100 ml; λ=589 nM)

rac-5-{2-Hidroxi-3-[1-(2-fluoro-5-trifluorometilfenil)-ciclopropil]-2-(hexin-1-il)-propionilamino}ftalida <u>10</u>

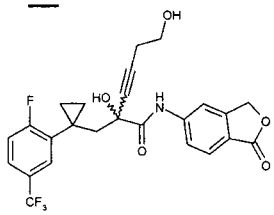


De modo análogo al Ejemplo 9 se sintetizó el compuesto 10.

^{1}H-RMN (ppm, $CDCl_3$, 400 MHz): 0,80-1,06 (7H), 1,30-1,50 (2H), 1,59 (2H), 2,10 (2H), 2,30 (1H), 2,52 (1H), 2,82 (1H),

5,28 (2H), 7,02 (1H), 7,30 (1H), 7,36 (1H), 7,57 (1H), 7,84 (1H), 7,95 (1H), 8,72 (1H).

rac-5-{2-Hidroxi-3-[1-(2-fluoro-5-trifluorometilfenil)-ciclopropil]-2-[(4-hidroxi)butin-1-il]-propionilamino}ftalida 11



Etapa A: La reacción de 4-(ter-butildimetilsililoxo)but-1-ina (175 mg), n-BuLi (0,59 ml, 1,6 M en hexano), 5-{3-[1-(2-fluoro-5-trifluorometilfenil)-ciclopropil]-2-oxopropionilamino}-ftalida (200 mg) en tetrahidrofurano análogamente al procedimiento descrito en el Ejemplo 9 dio como resultado 165 mg de producto.

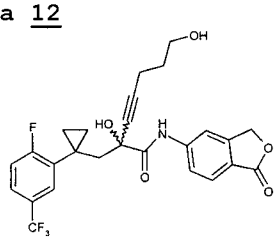
Etapa B: El producto obtenido en la Etapa A (160 mg) se disolvió en 5 ml de tetrahidrofurano. Se añadieron a 0 °C 270 µl de una solución 1 molar de fluoruro de tetrabutilamonio en tetrahidrofurano y se agitó durante 1 hora a 0 °C y durante otras 2 horas a 23 °C. Luego se vertió la mezcla de reacción en solución saturada acuosa de hidrógeno-carbonato de sodio. Se extrajo varias veces con acetato de etilo. Las fases orgánicas combinadas se lavaron con solución saturada de cloruro de sodio y se secaron sobre sulfato de sodio. Se

obtuvieron después de la cromatografía en columna en gel de sílice 77 mg de producto.

^{1}H-RMN (ppm, $CDCl_3$, 400 MHz): 0,83 (1H), 0,90-1,03 (3H), 2,20-2,40 (3H), 2,50 (1H), 3,39 (1H), 3,68 (2H), 5,25 (2H), 7,01 (1H), 7,32 (2H), 7,57 (1H), 7,82 (1H), 7,93 (1H), 8,91 (1H).

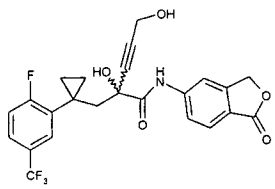
De modo análogo al Ejemplo 11 se prepararon a partir de 5-{3-[1-(2-fluoro-5-trifluorometilfenil)-ciclopropil]-2-oxopropionilamino}ftalida los compuestos 12 y 13:

rac-5-{2-Hidroxi-3-[1-(2-fluoro-5-trifluorometilfenil)-ciclopropil]-2-[(5-hidroxi)pentin-1-il]-propionilamino}ftalida 12



^{1}H-RMN (ppm, $CDCl_3$, 400 MHz): 0,83 (1H), 0,90-1,03 (3H), 1,70 (2H), 2,24 (2H), 2,33 (1H), 2,50 (1H), 3,09 (1H), 3,71 (2H), 5,26 (2H), 7,02 (1H), 7,35 (2H), 7,57 (1H), 7,83 (1H), 7,97 (1H), 8,82 (1H).

rac-5-{2-Hidroxi-3-[1-(2-fluoro-5-trifluorometilfenil)-ciclopropil]-2-[(3-hidroxi)propin-1-il]-propionilamino}ftalida 13



^{1}H-RMN (ppm, $CDCl_3$, 400 MHz): 0,84 (1H), 0,90-1,03 (3H), 2,37 (1H), 2,52 (1H), 3,25 (1H), 4,17 (2H), 5,27 (2H), 7,02 (1H), 7,30-7,40 (2H), 7,58 (1H), 7,83 (1H), 7,91 (1H), 8,77 (1H).

(+)-5-{2-Hidroxi-3-[1-(2-fluoro-5-trifluorometilfenil)-ciclopropil]-2-[(3-hidroxi)propin-1-il]-propionilamino}ftalida 13a y

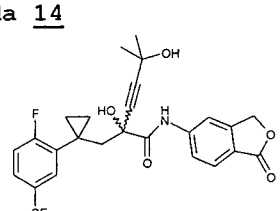
(-)-5-{2-hidroxi-3-[1-(2-fluoro-5-trifluorometilfenil)-ciclopropil]-2-[(3-hidroxi)propin-1-il]-propionilamino}ftalida 13b

La mezcla racémica descrita en el punto 13 (80 mg) se separó por HPLC quiral preparativa (columna Chiralpak AD 250 x 10 mm) en los enantiómeros 13a (35 mg) y 13b (37 mg).

13a : $[\alpha]^D_{20}$: + 28,3° ($CHCl_3$, 1,01 g/100 ml; λ=589 nM)

13b : $[\alpha]^D_{20}$: - 29,3° ($CHCl_3$, 1,08 g/100 ml; λ=589 nM)

rac-5-{2-Hidroxi-3-[1-(2-fluoro-5-trifluorometilfenil)-ciclopropil]-2-[(4-hidroxi-3-metil)butin-1-il]-propionilamino}ftalida 14

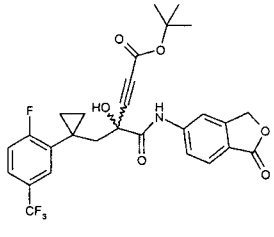


Etapa A: De modo análogo al Ejemplo 11 se hicieron reaccionar 300 mg de 5-{3-[1-(2-fluoro-5-trifluorometilfenil)-ciclopropil]-2-oxopropionilamino}ftalida y 282 mg de ter-butil-(1,1-dimetilprop-2-inil-oxi)-dimetilsilano. Se obtuvieron 15 mg de producto A.

Etapa B: Se disolvieron 70 mg del compuesto obtenido en A en 1 ml de diclorometano. Se añadieron a 0 °C 650 µl de ácido trifluoroacético (al 20% en diclorometano) y se agitó durante 3,5 horas a 0 °C. Luego se concentró al vacío hasta sequedad y el residuo se purificó por cromatografía en columna en gel de sílice. Se obtuvieron 27 mg de producto.

^{1}H-RMN (ppm, $CDCl_3$, 400 MHz): 0,82 (1H), 0,90-1,00 (2H), 1,04 (1H), 1,47 (6H), 2,28 (1H), 2,58 (1H), 3,08 (1H), 5,27 (2H), 7,03 (1H), 7,30 (1H), 7,36 (1H), 7,59 (1H), 7,83 (1H), 7,91 (1H), 8,78 (1H).

rac-5-{2-Hidroxi-3-[1-(2-fluoro-5-trifluorometilfenil)-ciclopropil]-2-(2-(ter-butilcarboxi)etin-1-il)-propionilamino}ftalida 15

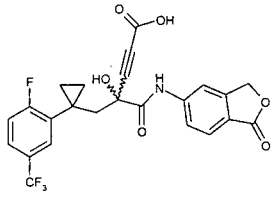


De modo análogo al Ejemplo 9 se sintetizó el compuesto 15.

^{1}H-RMN (ppm, $CDCl_3$, 400 MHz): 0,87 (1H), 0,93-1,05 (3H), 1,46 (9H), 2,42 (1H), 2,59 (1H), 3,39 (1H), 5,28 (2H), 7,03 (1H), 7,30-7,42 (2H), 7,57 (1H), 7,85 (1H), 7,92 (1H), 8,68 (1H).

rac-5-{2-Hidroxi-3-[1-(2-fluoro-5-trifluorometilfenil)-ciclopropil]-2-(2-carboxietin-1-il)-propionilamino}ftalida

16

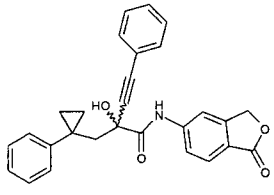


Se disolvieron 50 mg del compuesto descrito en el Ejemplo 15 en 5 ml de diclorometano. Se añadieron 100 µl de ácido trifluoroacético y se agitó durante 12 horas a 23 °C. Luego se concentró al vacío hasta sequedad y el residuo se purificó por cromatografía en columna en gel de sílice. Se obtuvieron 36 mg de producto.

^{1}H-RMN (ppm, DMSO-D_6, 300 MHz): 0,48 (1H), 0,78 (1H), 0,86 (1H), 1,09 (1H), 1,73 (1H), 2,89 (1H), 5,27 (2H), 6,62 (1H), 7,13 (1H), 7,31 (1H), 7,41 (1H), 7,53 (1H), 7,62 (1H), 7,68 (1H), 9,85 (1H).

De modo análogo al Ejemplo 3 se preparó a partir de 5-{3-[1-fenil-ciclopropil]-2-oxopropionilamino}ftalida el compuesto 17:

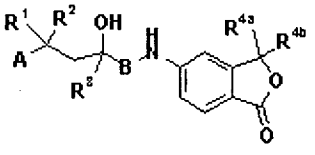
rac-5-{2-Hidroxi-3-[1-fenil-ciclopropil]-2-(fenil-etinil)propionilamino}-ftalida 17



^{1}H-RMN (ppm, $CDCl_3$, 400 MHz): 0,78 (1H), 0,90 (1H), 1,10-1,21 (2H), 2,38 (1H), 2,72 (1H), 2,77 (1H), 5,28 (2H), 7,18 (1H), 7,25-7,42 (6H), 7,41-7,52 (4H), 7,82 (1H), 8,06 (1H), 8,79 (1H).

REIVINDICACIONES

1. Compuestos de la fórmula general I



(I),

en donde

R^1 y R^2 son, de modo independiente entre sí, un átomo de hidrógeno, un grupo alquilo C_1-C_5 lineal o no lineal, ramificado o no ramificado, que además forma junto con el átomo de C de la cadena un anillo con un total de 3-7 miembros,

R^3 es un radical $C\equiv C-R^a$, en donde

R^a es un átomo de hidrógeno o un alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_{10}, heterocicloalquilo eventualmente mono- o polisustituido, igual o diferente, con K o un arilo o heteroarilo eventualmente mono- o polisustituido, igual o diferente, con L,

K es ciano, halógeno, hidroxi, nitro, $-C(O)R^b$, CO_2R^b, $-O-R^b$, $-S-R^b$, $SO_2NR^cR^d$, $-C(O)-NR^cR^d$, $-OC(O)-NR^cR^d$, $-C=NOR^b$ $-NR^cR^d$ o un cicloalquilo C_3-C_{10}, heterocicloalquilo eventualmente mono- o polisustituido, igual o diferente, con M o arilo o heteroarilo eventualmente mono- o polisustituido con L,

L es alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, perfluoroalquilo C_1-C_6, perfluoroalcoxi C_1-C_6, alcoxi C_1-C_6-alcoxi C_1-C_6, $(CH_2)_p$-cicloalquilo C_3-C_{10}, $(CH_2)_p$-heterocicloalquilo, $(CH_2)_pCN$, $(CH_2)_pHal$, $(CH_2)_pNO_2$, $(CH_2)_p$-arilo C_6-C_{12}, $(CH_2)_p$-heteroarilo,

$-(CH_2)_pPO_3(R^b)_2$,

$-(CH_2)_pNR^cR^d$, $-(CH_2)_pNR^eCOR^b$,

$-(CH_2)_pNR^eCSR^b$, $-(CH_2)_pNR^eS(O)R^b$,

$-(CH_2)_pNR^eS(O)_2R^b$,

$-(CH_2)_pNR^eCONR^cR^d$,

$-(CH_2)_pNR^eCOOR^b$,

$-(CH_2)_pNR^eC(NH)NR^cR^d$,

$-(CH_2)_pNR^eCSNR^cR^d$,

$-(CH_2)_pNR^eS(O)NR^cR^d$,

$-(CH_2)_pNR^eS(O)_2NR^cR^d$, $-(CH_2)_pCOR^b$,

$-(CH_2)_pCSR^b$, $-(CH_2)_pS(O)R^b$,

$-(CH_2)_pS(O)(NH)R^b$, $-(CH_2)_pS(O)_2R^b$,

$-(CH_2)_pS(O)_2NR^cR^d$, $-(CH_2)_pSO_2OR^b$,

$-(CH_2)_pCO_2R^b$, $-(CH_2)_pCONR^cR^d$,

$-(CH_2)_pCSNR^cR^d$, $-(CH_2)_pOR^b$,

$-(CH_2)_pSR^b$, $-(CH_2)_pCR^b(OH)-R^e$,

$-(CH_2)_p-C=NOR^b$, $-O-(CH_2)_n-O-$,

$-O-(CH_2)_n-CH_2-$, $-O-CH=CH-$ o

$-(CH_2)_{n+2}-$, en donde es n = 1 ó 2 y los átomos de oxígeno y/o átomos de carbono terminales están unidos con átomos de carbono del anillo directamente adyacentes,

M es alquilo C_1-C_6 o un grupo $-COR^b$, CO_2R^b, $-O-R^b$ o $-NR^cR^d$, en donde

R^b es un átomo de hidrógeno o un alquilo C_1-C_6, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_{10}, arilo C_6-C_{12} o perfluoroalquilo C_1-C_3 y

R^c y R^d son, de modo independiente entre sí, un átomo de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_{10}, arilo C_6-C_{12}, $C(O)R^b$ o un grupo hidroxi, en donde cuando

R^c es un grupo hidroxi, R^d sólo puede ser un átomo de hidrógeno, un alquilo C_1-C_6, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_{10} o arilo C_6-C_{12} y viceversa, así como

R^e es un átomo de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_{10} o arilo C_6-C_{12} y

p puede ser una cifra de 0 a 6,

o

R^3 es un radical $C=C-R^gR^h$, en donde

R^g y R^h son, de modo independiente entre sí, un átomo de hidrógeno o un alquilo C_1-C_8, alquenilo C_2-C_8 o alquinilo C_2-C_8 eventualmente mono- o polisustituido, igual o diferente, con X, en donde

X es un ciano, halógeno, hidroxi, nitro, $-C(O)R^b$, CO_2R^b, $-O-R^b$, $-C(O)-NR^cR^d$, $-NR^cR^d$ con los significados ya mencionados más arriba para R^b, R^c y R^d y

R^{4a} y R^{4b} son, de modo independiente entre sí, un átomo de hidrógeno, un alquilo C_1-C_4, un alquenilo C_2-C_4 o forman, junto con el átomo de carbono del anillo, un anillo de 3-6 miembros,

A es un anillo aromático carbocíclico o heterocíclico mono- o bicíclico, que puede estar eventualmente mono- o polisustituido con alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, perfluoroalquilo C_1-C_6, perfluoroalcoxi C_1-C_6, alcoxi C_1-C_6-alquilo C_1-C_6, alcoxi C_1-C_6-alcoxi C_1-C_6, $(CH_2)_p$-cicloalquilo C_3-C_{10}, $(CH_2)_p$-heterocicloalquilo, $(CH_2)_pCN$, $(CH_2)_pHal$, $(CH_2)_pNO_2$, $(CH_2)_p$-arilo C_6-C_{12}, $(CH_2)_p$-heteroarilo, $-(CH_2)_pPO_3(R^b)_2$, $-(CH_2)_pNR^cR^d$, $-(CH_2)_pNR^eCOR^b$, $-(CH_2)_pNR^eCSR^b$, $-(CH_2)_pNR^eS(O)R^b$, $-(CH_2)_pNR^eS(O)_2R^b$,

$-(CH_2)_pNR^eCONR^cR^d$, $-(CH_2)_pNR^eCOOR^b$,

$-(CH_2)_pNR^eC(NH)NR^cR^d$, $-(CH_2)_pNR^eCSNR^cR^d$,

$-(CH_2)_pNR^eS(O)NR^cR^d$, $-(CH_2)_pNR^eS(O)_2NR^cR^d$,

$-(CH_2)_pCOR^b$, $-(CH_2)_pCSR^b$, $-(CH_2)_p\ S(O)R^b$,

$-(CH_2)_pS(O)(NH)R^b$, $-(CH_2)_pS(O)_2R^b$,

$-(CH_2)_pS(O)_2NR^cR^d$, $-(CH_2)_pSO_2OR^b$, $-(CH_2)_pCO_2R^b$,

$-(CH_2)_pCONR^cR^d$, $-(CH_2)_pCSNR^cR^d$, $-(CH_2)_pOR^b$,

$-(CH_2)_pSR^b$, $-(CH_2)_pCR^b(OH)-R^d$, $-(CH_2)_p-C=NOR^b$,

$-O-(CH_2)_n-O-$, $-O-(CH_2)_n-CH_2-$, $-O-CH=CH-$ o

$-(CH_2)_{n+2}-$, en donde es n = 1 ó 2 y los átomos de oxígeno y/o átomos de carbono están unidos con átomos de carbono del anillo directamente adyacentes o

A es un radical $-CO_2R^b$, $C(O)NR^cR^d$, COR^b,

o

A es un grupo alquenilo $-CR^5=CR^6R^7$, en donde R^5, R^6 y R^7 son iguales o diferentes y, de modo independiente entre sí, son átomos de hidrógeno, átomos de halógeno, radicales arilo o un grupo alquilo C_1-C_5 no sustituido o parcial o totalmente fluorado o

A es un grupo alquinilo $-C\equiv CR^5$, con el significado indicado arriba para R^5 y

B es un grupo carbonilo o un grupo CH_2,

así como sus sales farmacéuticamente aceptables.

2. Compuestos de acuerdo con la reivindicación 1, en donde R^1 y R^2 son preferentemente un átomo de hidrógeno, un grupo metilo o etilo.

3. Compuestos de acuerdo con la reivindicación 1, en donde R^1 y R^2 forman con preferencia, junto con el átomo de C de la cadena, un anillo con un total de 3-7 miembros.

4. Compuestos de acuerdo con la reivindicación 1 a 3, en donde R^3 es preferentemente alquenilo, alquinilo, arilalquinilo, heteroarilalquinilo, cicloalquilalquinilo, heterocicloalquilalquinilo.

5. Compuestos de acuerdo con una de las reivindicaciones precedentes, en donde R^3 es preferentemente un grupo vinilo, etinilo, propinilo, butinilo, pentinilo, hexinilo, heptinilo, octinilo, hidroxipropinilo, hidroxibutinilo, 3-hidroxi-3-metilbutinilo, hidroxipentinilo, carboxipropinilo, t-butilcarboxipropinilo, feniletinilo, (hidroxifenil)etinilo, (metoxifenil)etinilo, (dimetilaminofenil)etinilo, (metilfenil)etinilo, (cianofenil)etinilo, (trifluorometil)etinilo, (difenil)etinilo, (nitrofenil)etinilo, (ter-butilfenil)etinilo, (acetilfenil)etinilo, (acetoxifenil)etinilo, (carboxifenil)etinilo o benciletinilo.

6. Compuestos de acuerdo con una de las reivindicaciones precedentes, en donde A es preferentemente un anillo aromático.

7. Compuestos de acuerdo con una de las reivindicaciones precedentes, en donde A es preferentemente un radical fenilo o naftilo.

8. Compuestos de acuerdo con la reivindicación 7, en donde A es preferentemente un radical fenilo no sustituido o eventualmente mono- o polisustituido.

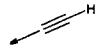
9. Compuestos de acuerdo con la reivindicación 8, en donde el radical fenilo está sustituido preferentemente con uno o dos átomos de halógeno o un grupo trifluorometilo.

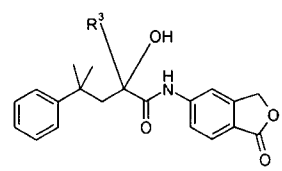
10. Compuestos de acuerdo con la reivindicación 9, en donde los átomos de halógeno son preferentemente cloro y/o flúor.

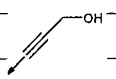
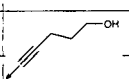
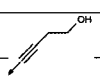
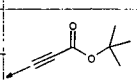
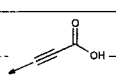
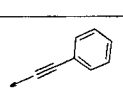
11. Compuestos de acuerdo con las reivindicaciones 1-8, en donde A es preferentemente un anillo fenilo sustituido con $-O-(CH_2)_n-O-$ u $-O-(CH_2)_n-CH_2-$, en donde los átomos de carbono del anillo directamente adyacentes están unidos.

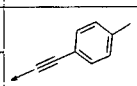
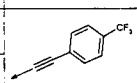
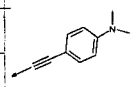
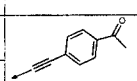
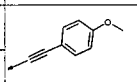
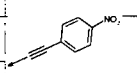
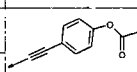
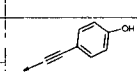
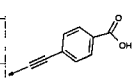
12. Compuestos de acuerdo con una de las reivindicaciones precedentes, en donde R^{4a} y R^{4b} son en cada caso, de modo independiente entre sí, un átomo de hidrógeno.

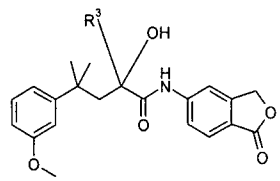
13. Compuestos de acuerdo con la reivindicación 1 a 12, a saber

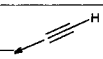
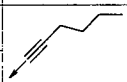
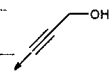
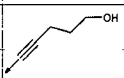
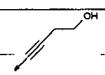
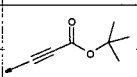
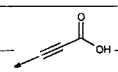
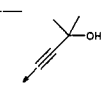
N.°	Racémico o enantiómero	R3
1	rac	

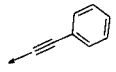
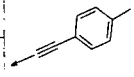
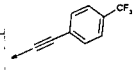
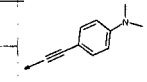
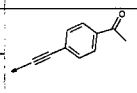
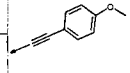
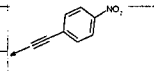
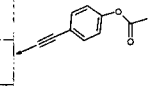
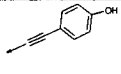
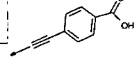


2	+	
3	–	
4	rac	
5	+	
6	–	
7	rac	
8	+	
9	–	
10	rac	
11	+	
12	–	
13	rac	
14	+	
15	–	
16	rac	
17	+	
18	–	
19	rac	
20	+	
21	–	
22	rac	
23	+	
24	–	
25	rac	
26	+	
27	–	
28	rac	
29	+	
30	–	
31	rac	

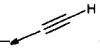
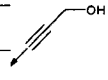
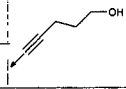
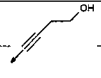
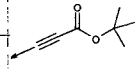
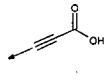
32	+	
33	–	
34	rac	
35	+	
36	–	
37	rac	
38	+	
39	–	
40	rac	
41	+	
42	–	
43	rac	
44	+	
45	–	
46	rac	
47	+	
48	–	
49	rac	
50	+	
51	–	
52	rac	
53	+	
54	–	
55	rac	
56	+	
57	–	
58	rac	
59	+	
60	–	

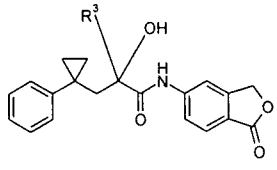


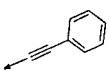
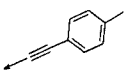
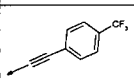
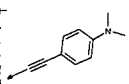
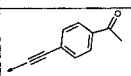
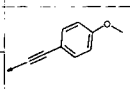
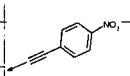
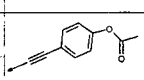
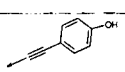
N.º	Racémico o enantiómero	R3
61	rac	
62	+	
63	–	
64	rac	
65	+	
66	–	
67	rac	
68	+	
69	–	
70	rac	
71	+	
72	–	
73	rac	
74	+	
75	–	
76	rac	
77	+	
78	–	
79	rac	
80	+	
81	–	
82	rac	
83	+	
84	–	
85	rac	
86	+	
87	–	
88	rac	

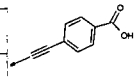
89	+	
90	–	
91	rac	
92	+	
93	–	
94	rac	
95	+	
96	–	
97	rac	
98	+	
99	–	
100	rac	
101	+	
102	–	
103	rac	
104	+	
105	–	
106	rac	
107	+	
108	–	
109	rac	
110	+	
111	–	
112	rac	
113	+	
114	–	
115	rac	
116	+	
117	–	
118	rac	

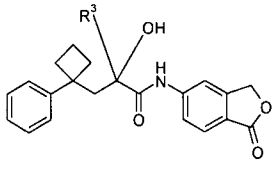
119	+
120	–

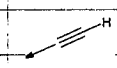
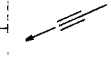
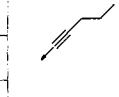
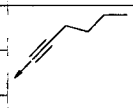
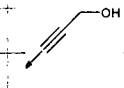
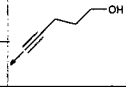
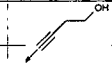
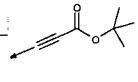
N.º	Racémico o enantiómero	R3
121	rac	
122	+	
123	–	
124	rac	
125	+	
126	–	
127	rac	
128	+	
129	–	
130	rac	
131	+	
132	–	
133	rac	
134	+	
135	–	
136	rac	
137	+	
138	–	
139	rac	
140	+	
141	–	
142	rac	
143	+	
144	–	
145	rac	

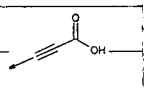
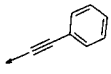
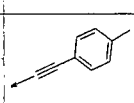
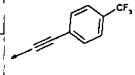
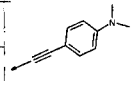
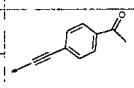
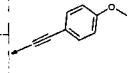
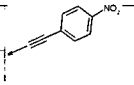
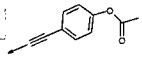


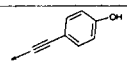
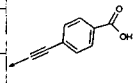
146	+	
147	–	
148	rac	
149	+	
150	–	
151	rac	
152	+	
153	–	
154	rac	
155	+	
156	–	
157	rac	
158	+	
159	–	
160	rac	
161	+	
162	–	
163	rac	
164	+	
165	–	
166	rac	
167	+	
168	–	
169	rac	
170	+	
171	–	
172	rac	
173	+	
174	–	
175	rac	

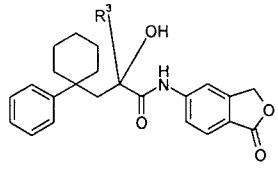
176	+	
177	-	
178	rac	
179	+	
180	-	

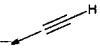
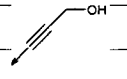
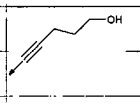


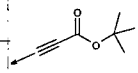
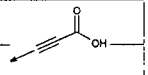
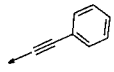
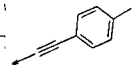
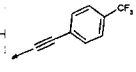
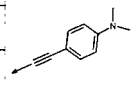
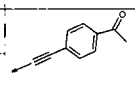
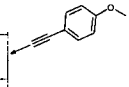
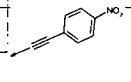
N.º	Racémico o enantiómero	R3
181	rac	
182	+	
183	-	
184	rac	
185	+	
186	-	
187	rac	
188	+	
189	-	
190	rac	
191	+	
192	-	
193	rac	
194	+	
195	-	
196	rac	
197	+	
198	-	
199	rac	
200	+	
201	-	
202	rac	

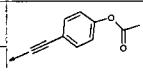
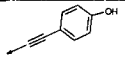
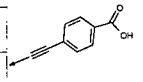
203	+	
204	–	
205	rac	
206	+	
207	–	
208	rac	
209	+	
210	–	
211	rac	
212	+	
213	–	
214	rac	
215	+	
216	–	
217	rac	
218	+	
219	–	
220	rac	
221	+	
222	–	
223	rac	
224	+	
225	–	
226	rac	
227	+	
228	–	
229	rac	
230	+	
231	–	
232	rac	

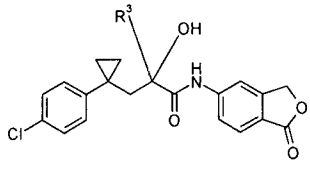
233	+	
234	-	
235	rac	
236	+	
237	-	
238	rac	
239	+	
240	-	

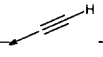
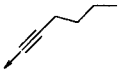
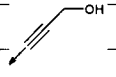
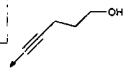


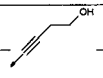
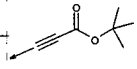
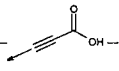
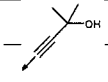
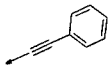
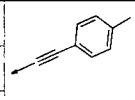
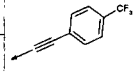
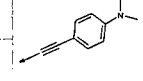
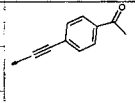
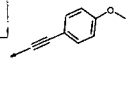
N.°	Racémico o enantiómero	R3
241	rac	
242	+	
243	-	
244	rac	
245	+	
246	-	
247	rac	
248	+	
249	-	
250	rac	
251	+	
252	-	
253	rac	
254	+	
255	-	
256	rac	
257	+	
258	-	
259	rac	

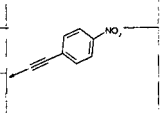
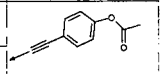
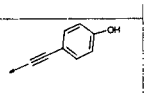
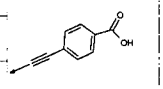
260	+	
261	-	
262	rac	
263	+	
264	-	
265	rac	
266	+	
267	-	
268	rac	
269	+	
270	-	
271	rac	
272	+	
273	-	
274	rac	
275	+	
276	-	
277	rac	
278	+	
279	-	
280	rac	
281	+	
282	-	
283	rac	
284	+	
285	-	
286	rac	
287	+	
288	-	
289	rac	

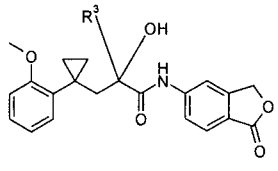
290	+	
291	–	
292	rac	
293	+	
294	–	
295	rac	
296	+	
297	–	
298	rac	
299	+	
300	–	

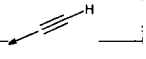
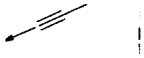
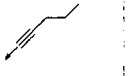
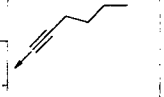
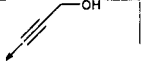


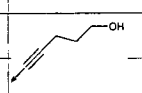
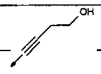
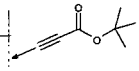
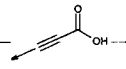
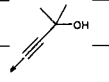
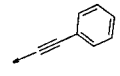
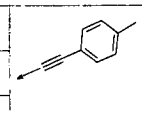
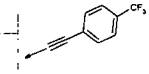
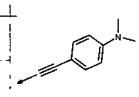
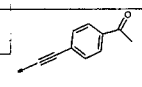
N.°	Racémico o enantiómero	R3
301	rac	
302	+	
303	–	
304	rac	
305	+	
306	–	
307	rac	
308	+	
309	–	
310	rac	
311	+	
312	–	
313	rac	
314	+	
315	–	
316	rac	

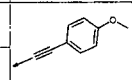
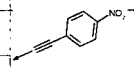
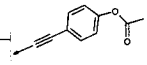
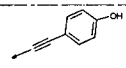
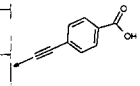
317	+	
318	–	
319	rac	
320	+	
321	–	
322	rac	
323	+	
324	–	
325	rac	
326	+	
327	–	
328	rac	
329	+	
330	–	
331	rac	
332	+	
333	–	
334	rac	
335	+	
336	–	
337	rac	
338	+	
339	–	
340	rac	
341	+	
342	–	
343	rac	
344	+	
345	–	
346	rac	

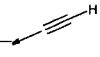
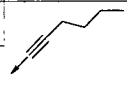
347	+	
348	-	
349	rac	
350	+	
351	-	
352	rac	
353	+	
354	-	
355	rac	
356	+	
357	-	
358	rac	
359	+	
360	-	

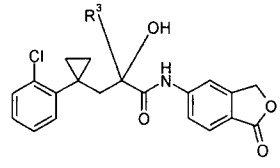


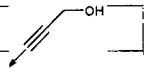
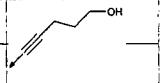
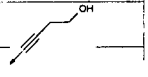
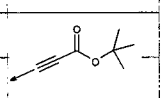
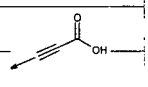
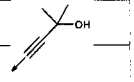
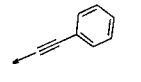
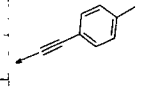
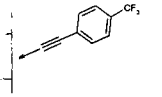
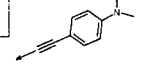
N.°	Racémico o enantiómero	R3
361	rac	
362	+	
363	-	
364	rac	
365	+	
366	-	
367	rac	
368	+	
369	-	
370	rac	
371	+	
372	-	
373	rac	

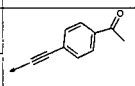
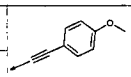
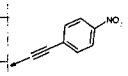
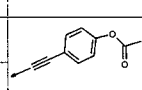
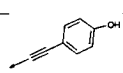
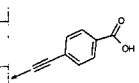
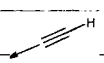
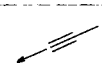
374	+	
375	–	
376	rac	
377	+	
378	–	
379	rac	
380	+	
381	–	
382	rac	
383	+	
384	–	
385	rac	
386	+	
387	–	
388	rac	
389	+	
390	–	
391	rac	
392	+	
393	–	
394	rac	
395	+	
396	–	
397	rac	
398	+	
399	–	
400	rac	
401	+	
402	–	
403	rac	

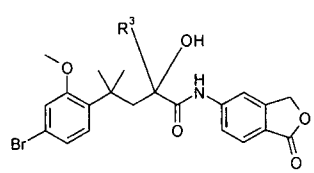
404	+	
405	–	
406	rac	
407	+	
408	–	
409	rac	
410	+	
411	–	
412	rac	
413	+	
414	–	
415	rac	
416	+	
417	–	
418	rac	
419	+	
420	–	

N.°	Racémico o enantiómero	R3
421	rac	
422	+	
423	–	
424	rac	
425	+	
426	–	
427	rac	
428	+	
429	–	
430	rac	

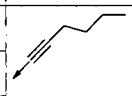
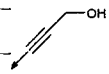
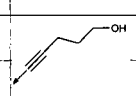
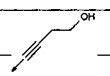
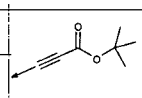
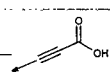
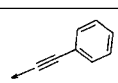
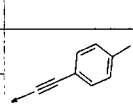
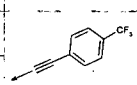


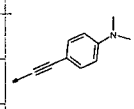
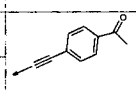
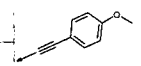
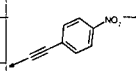
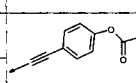
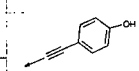
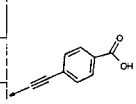
431	+	
432	–	
433	rac	
434	+	
435	–	
436	rac	
437	+	
438	–	
439	rac	
440	+	
441	–	
442	rac	
443	+	
444	–	
445	rac	
446	+	
447	–	
448	rac	
449	+	
450	–	
451	rac	
452	+	
453	–	
454	rac	
455	+	
456	–	
457	rac	
458	+	
459	–	
460	rac	

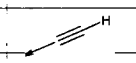
461	+	
462	–	
463	rac	
464	+	
465	–	
466	rac	
467	+	
468	–	
469	rac	
470	+	
471	–	
472	rac	
473	+	
474	–	
475	rac	
476	+	
477	–	
478	rac	
479	+	
480	–	
N.°	Racémico o enantiómero	R3
481	rac	
482	+	
483	–	
484	rac	
485	+	
486	–	
487	rac	
488	+	

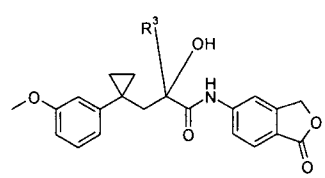


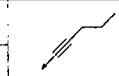
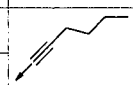
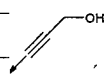
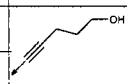
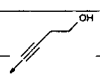
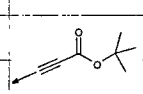
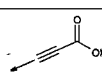
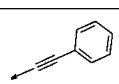
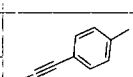
320

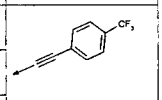
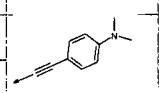
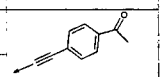
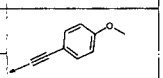
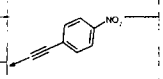
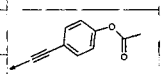
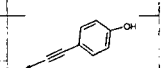
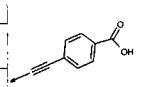
489	–	
490	rac	
491	+	
492	–	
493	rac	
494	+	
495	–	
496	rac	
497	+	
498	–	
499	rac	
500	+	
501	–	
502	rac	
503	+	
504	–	
505	rac	
506	+	
507	–	
508	rac	
509	+	
510	–	
511	rac	
512	+	
513	–	
214	rac	
515	+	
516	–	
517	rac	
518	+	

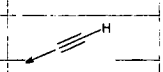
519	–	
520	rac	
521	+	
522	–	
523	rac	
524	+	
525	–	
526	rac	
227	+	
528	–	
529	rac	
530	+	
531	–	
532	rac	
533	+	
534	–	
535	rac	
536	+	
537	–	
538	rac	
539	+	
540	–	

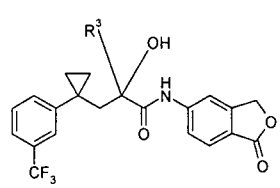
N.°	Racémico o enantiómero	R3
541	rac	
542	+	
543	–	
544	rac	
545	+	

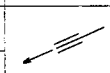
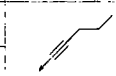
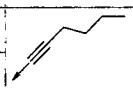
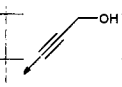
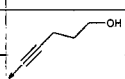
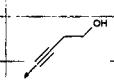
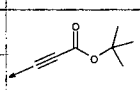
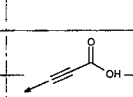
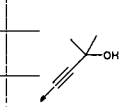
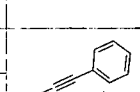


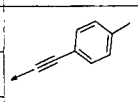
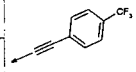
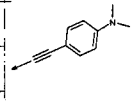
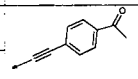
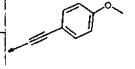
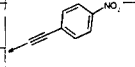
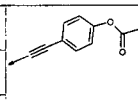
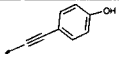
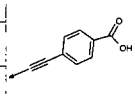
546	–	
547	rac	
548	+	
549	–	
550	rac	
551	+	
552	–	
553	rac	
554	+	
555	–	
556	rac	
557	+	
558	–	
559	rac	
560	+	
561	–	
562	rac	
563	+	
564	–	
565	rac	
566	+	
567	–	
568	rac	
569	+	
570	–	
571	rac	
572	+	
573	–	
574	rac	
575	+	

576	–	
577	rac	
578	+	
579	–	
580	rac	
581	+	
582	–	
583	rac	
584	+	
585	–	
586	rac	
587	+	
588	–	
589	rac	
590	+	
591	–	
592	rac	
593	+	
594	–	
595	rac	
596	+	
597	–	
598	rac	
599	+	
600	–	

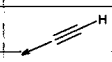
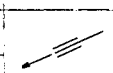
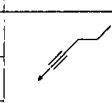
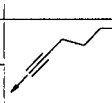
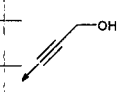
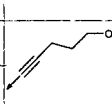
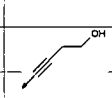
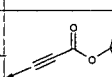
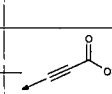
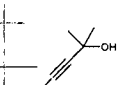
N.º	Racémico o enantiómero	R3
601	rac	
602	+	

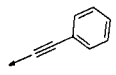
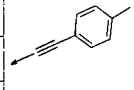
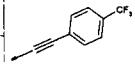
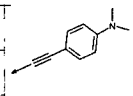
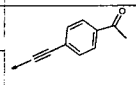
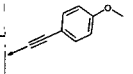
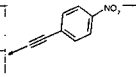
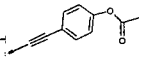
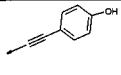
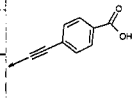


603	-	
604	rac	
605	+	
606	-	
607	rac	
608	+	
609	-	
610	rac	
611	+	
612	-	
613	rac	
614	+	
615	-	
616	rac	
617	+	
618	-	
619	rac	
620	+	
621	-	
622	rac	
623	+	
624	-	
625	rac	
626	+	
627	-	
628	rac	
629	+	
630	-	
631	rac	
632	+	

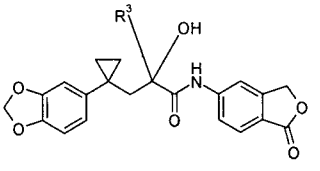
633	-	
634	rac	
635	+	
636	-	
637	rac	
638	+	
639	-	
640	rac	
641	+	
642	-	
643	rac	
644	+	
645	-	
646	rac	
647	+	
648	-	
649	rac	
650	+	
651	-	
652	rac	
653	+	
654	-	
655	rac	
656	+	
657	-	
658	rac	
659	+	
660	-	

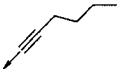
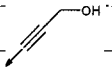
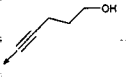
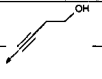
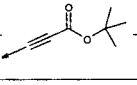
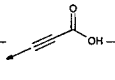
N.º	Racémico o	R3

	enantiómero	
661	rac	
662	+	
663	–	
664	rac	
665	+	
666	–	
667	rac	
668	+	
669	–	
670	rac	
671	+	
672	–	
673	rac	
674	+	
675	–	
676	rac	
677	+	
678	–	
679	rac	
680	+	
681	–	
682	rac	
683	+	
684	–	
685	rac	
686	+	
687	–	
688	rac	
689	+	

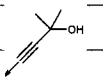
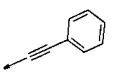
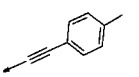
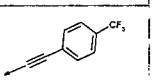
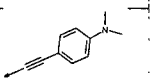
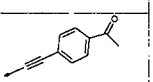
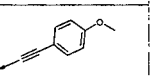
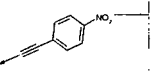
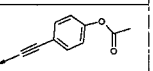
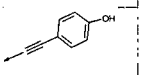
690	–	
691	rac	
692	+	
693	–	
694	rac	
695	+	
696	–	
697	rac	
698	+	
699	–	
700	rac	
701	+	
702	–	
703	rac	
704	+	
705	–	
706	rac	
707	+	
708	–	
709	rac	
710	+	
711	–	
712	rac	
713	+	
714	–	
715	rac	
716	+	
717	–	
718	rac	
719	+	

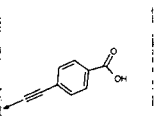
720	-

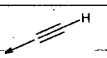
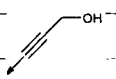
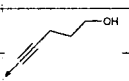
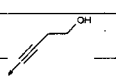
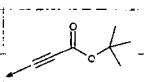


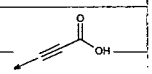
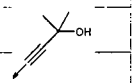
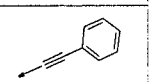
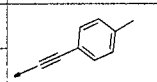
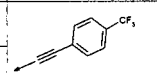
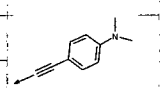
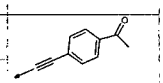
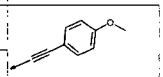
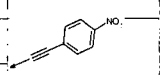
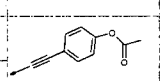
N.°	Racémico o enantiómero	R3
721	rac	
722	+	
723	-	
724	rac	
725	+	
726	-	
727	rac	
728	+	
729	-	
730	rac	
731	+	
732	-	
733	rac	
734	+	
735	-	
736	rac	
737	+	
738	-	
739	rac	
740	+	
741	-	
742	rac	
743	+	
744	-	
745	rac	
746	+	

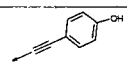
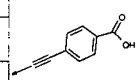
380

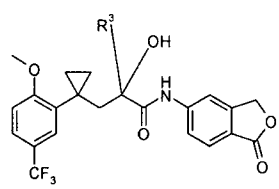
747	-	
748	rac	
749	+	
750	-	
751	rac	
752	+	
753	-	
754	rac	
755	+	
756	-	
757	rac	
758	+	
759	-	
760	rac	
761	+	
762	-	
763	rac	
764	+	
765	-	
766	rac	
767	+	
768	-	
769	rac	
770	+	
771	-	
772	rac	
773	+	
774	-	
775	rac	
776	+	

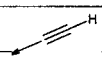
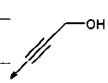
777	-	
778	rac	
779	+	
780	-	

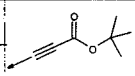
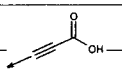
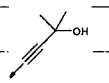
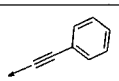
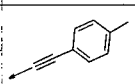
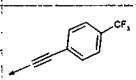
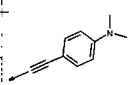
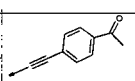
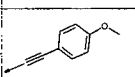
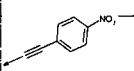
N.°	Racémico o enantiómero	R3
781	rac	
782	+	
783	-	
784	rac	
785	+	
786	-	
787	rac	
788	+	
789	-	
790	rac	
791	+	
792	-	
793	rac	
794	+	
795	-	
796	rac	
797	+	
798	-	
799	rac	
800	+	
801	-	
802	rac	
803	+	

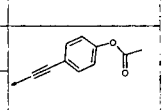
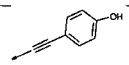
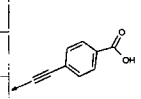
804	–	
805	rac	
806	+	
807	–	
808	rac	
809	+	
810	–	
811	rac	
812	+	
813	–	
814	rac	
815	+	
816	–	
817	rac	
818	+	
819	–	
820	rac	
821	+	
822	–	
823	rac	
824	+	
825	–	
826	rac	
827	+	
828	–	
829	rac	
830	+	
831	–	
832	rac	
833	+	

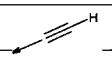
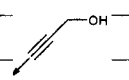
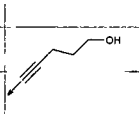
834	–	
835	rac	
836	+	
837	–	
838	rac	
839	+	
840	–	

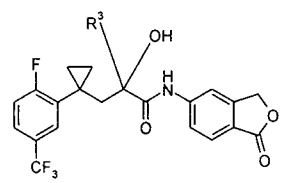


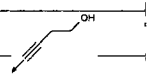
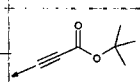
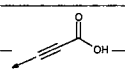
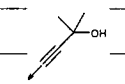
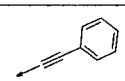
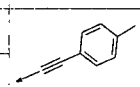
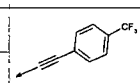
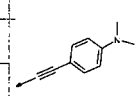
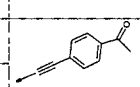
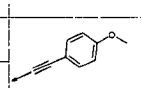
N.°	Racémico o enantiómero	R3
841	rac	
842	+	
843	–	
844	rac	
845	+	
846	–	
847	rac	
848	+	
849	–	
850	rac	
851	+	
852	–	
853	rac	
854	+	
855	–	
856	rac	
857	+	
858	–	
859	rac	
860	+	

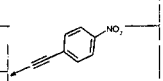
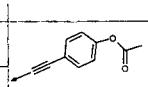
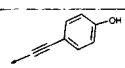
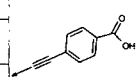
861	-	
862	rac	
863	+	
864	-	
865	rac	
866	+	
867	-	
868	rac	
869	+	
870	-	
871	rac	
872	+	
873	-	
874	rac	
875	+	
876	-	
877	rac	
878	+	
879	-	
880	rac	
881	+	
882	-	
883	rac	
884	+	
885	-	
886	rac	
887	+	
888	-	
889	rac	
890	+	

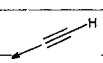
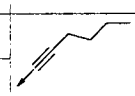
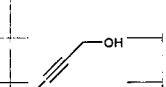
891	-	
892	rac	
893	+	
894	-	
895	rac	
896	+	
897	-	
898	rac	
899	+	
900	-	

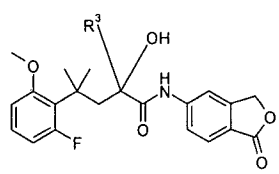
N.°	Racémico o enantiómero	R3
901	rac	
902	+	
903	-	
904	rac	
905	+	
906	-	
907	rac	
908	+	
909	-	
910	rac	
911	+	
912	-	
913	rac	
914	+	
915	-	
916	rac	
917	+	

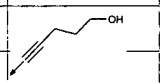
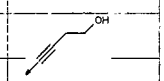
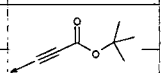
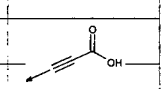
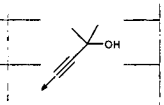
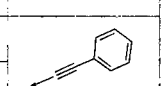
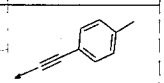
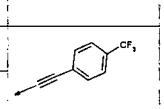
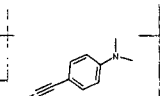
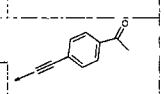


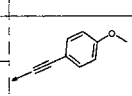
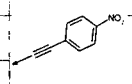
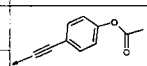
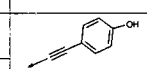
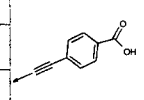
918	-	
919	rac	
920	+	
921	-	
922	rac	
923	+	
924	-	
925	rac	
926	+	
927	-	
928	rac	
929	+	
930	-	
931	rac	
932	+	
933	-	
934	rac	
935	+	
936	-	
937	rac	
938	+	
939	--	
940	rac	
941	+	
942	-	
943	rac	
944	+	
945	-	
946	rac	
947	+	

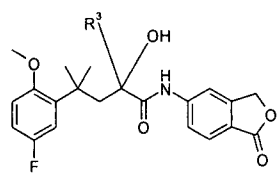
948	-	
949	rac	
950	+	
951	-	
952	rac	
953	+	
954	-	
955	rac	
956	+	
957	-	
958	rac	
959	+	
960	-	

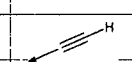
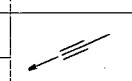
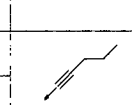
N.°	Racémico o enantiómero	R3
961	rac	
962	+	
963	-	
964	rac	
965	+	
966	-	
967	rac	
968	+	
969	-	
970	rac	
971	+	
972	-	
973	rac	
974	+	



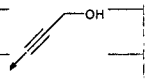
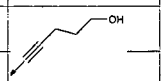
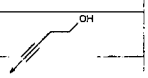
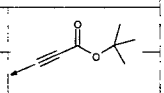
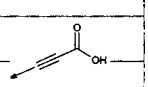
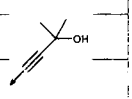
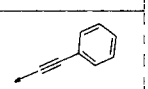
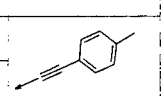
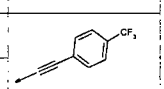
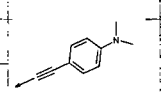
975	–	
976	rac	
977	+	
978	–	
979	rac	
980	+	
981	–	
982	rac	
983	+	
984	–	
985	rac	
986	+	
987	–	
988	rac	
989	+	
990	–	
991	rac	
992	+	
993	–	
994	rac	
995	+	
996	–	
997	rac	
998	+	
999	–	
1000	rac	
1001	+	
1002	–	
1003	rac	
1004	+	

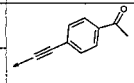
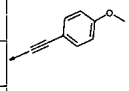
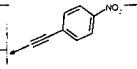
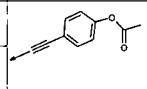
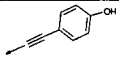
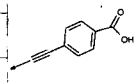
1005	–	
1006	rac	
1007	+	
1008	–	
1009	rac	
1010	+	
1011	–	
1012	rac	
1013	+	
1014	–	
1015	rac	
1016	+	
1017	–	
1018	rac	
1019	+	
1020	–	



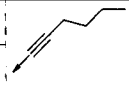
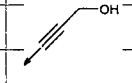
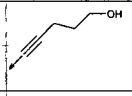
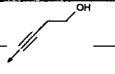
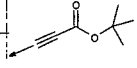
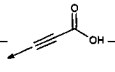
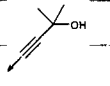
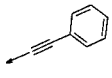
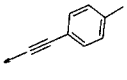
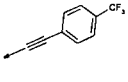
N.°	Racémico o enantiómero	R3
1021	rac	
1022	+	
1023	–	
1024	rac	
1025	+	
1026	–	
1027	rac	
1028	+	
1029	–	
1030	rac	
1031	+	

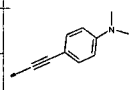
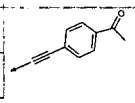
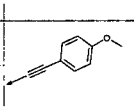
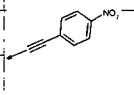
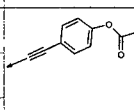
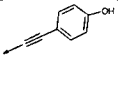
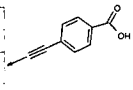
390

1032	-	
1033	rac	
1034	+	
1035	-	
1036	rac	
1037	+	
1038	-	
1039	rac	
1040	+	
1041	-	
1042	rac	
1043	+	
1044	-	
1045	rac	
1046	+	
1047	-	
1048	rac	
1049	+	
1050	-	
1051	rac	
1052	+	
1053	-	
1054	rac	
1055	+	
1056	-	
1057	rac	
1058	+	
1059	-	
1060	rac	
1061	+	

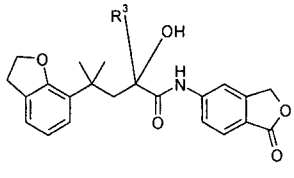
1062	-	
1063	rac	
1064	+	
1065	-	
1066	rac	
1067	+	
1068	-	
1069	rac	
1070	+	
1071	-	
1072	rac	
1073	+	
1074	-	
1075	rac	
1076	+	
1077	-	
1078	rac	
1079	+	
1080	-	

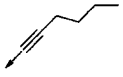
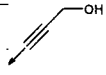
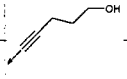
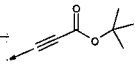
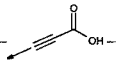
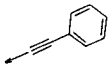
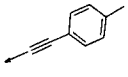
N.°	Racémico o enantiómero	R3
1081	rac	
1082	+	
1083	-	
1084	rac	
1085	+	
1086	-	
1087	rac	
1088	+	

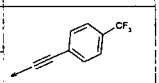
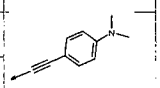
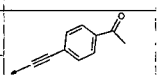
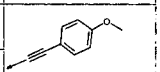
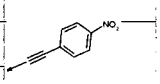
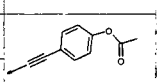
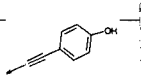
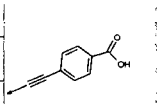
1089	-	
1090	rac	
1091	+	
1092	-	
1093	rac	
1094	+	
1095	-	
1096	rac	
1097	+	
1098	-	
1099	rac	
1100	+	
1101	-	
1102	rac	
1103	+	
1104	-	
1105	rac	
1106	+	
1107	-	
1108	rac	
1109	+	
1110	-	
1111	rac	
1112	+	
1113	-	
1114	rac	
1115	+	
1116	-	
1117	rac	
1118	+	

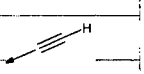
1119	-	
1120	rac	
1121	+	
1122	-	
1123	rac	
1124	+	
1125	-	
1126	rac	
1127	+	
1128	-	
1129	rac	
1130	+	
1131	-	
1132	rac	
1133	+	
1134	-	
1135	rac	
1136	+	
1137	-	
1138	rac	
1139	+	
1140	-	

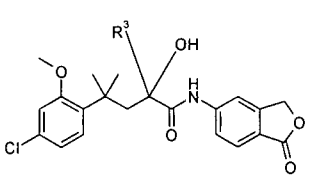
N.º	Racémico o enantiómero	R3
1141	rac	
1142	+	
1143	-	
1144	rac	
1145	+	

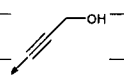
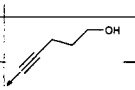
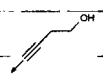
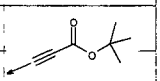
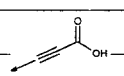
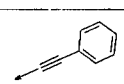


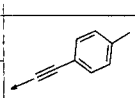
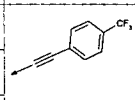
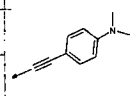
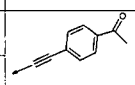
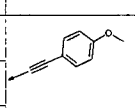
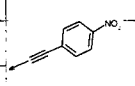
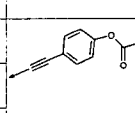
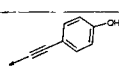
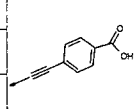
1146	-	
1147	rac	
1148	+	
1149	-	
1150	rac	
1151	+	
1152	-	
1153	rac	
1154	+	
1155	-	
1156	rac	
1157	+	
1158	-	
1159	rac	
1160	+	
1161	-	
1162	rac	
1163	+	
1164	-	
1165	rac	
1166	+	
1167	-	
1168	rac	
1169	+	
1170	-	
1171	rac	
1172	+	
1173	-	
1174	rac	
1175	+	

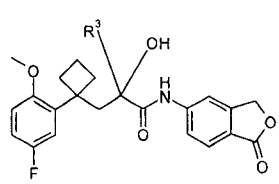
1176	–	
1177	rac	
1178	+	
1179	–	
1180	rac	
1181	+	
1182	–	
1183	rac	
1184	+	
1185	–	
1186	rac	
1187	+	
1188	–	
1189	rac	
1190	+	
1191	–	
1192	rac	
1193	+	
1194	–	
1195	rac	
1196	+	
1197	–	
1198	rac	
1199	+	
1200	–	

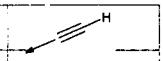
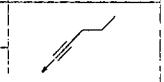
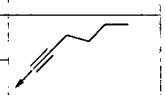
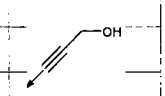
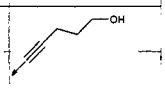
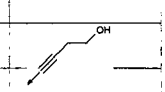
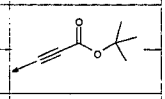
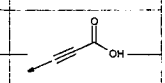
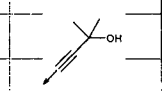
N.º	Racémico o enantiómero	R3
1201	rac	
1202	+	



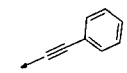
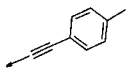
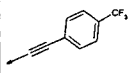
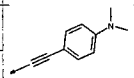
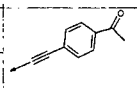
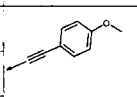
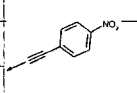
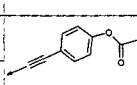
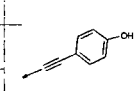
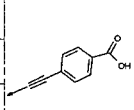
1203	–	
1204	rac	
1205	+	
1206	–	
1207	rac	
1208	+	
1209	–	
1210	rac	
1211	+	
1212	–	
1213	rac	
1214	+	
1215	–	
1216	rac	
1217	+	
1218	–	
1219	rac	
1220	+	
1221	–	
1222	rac	
1223	+	
1224	–	
1225	rac	
1226	+	
1227	–	
1228	rac	
1229	+	
1230	–	
1231	rac	
1232	+	

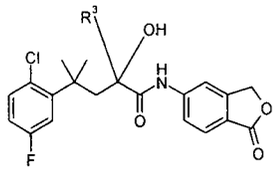
1233	-	
1234	rac	
1235	+	
1236	-	
1237	rac	
1238	+	
1239	-	
1240	rac	
1241	+	
1242	-	
1243	rac	
1244	+	
1245	-	
1246	rac	
1247	+	
1248	-	
1249	rac	
1250	+	
1251	-	
1252	rac	
1253	+	
1254	-	
1255	rac	
1256	+	
1257	-	
1258	rac	
1259	+	
1260	-	
N.°	Racémico o enantiómero	R3

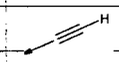
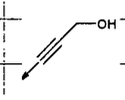
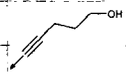
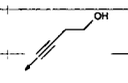
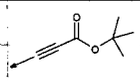
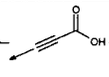


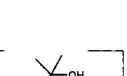
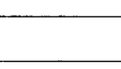
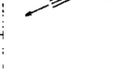
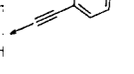
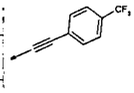
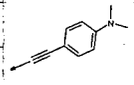
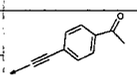
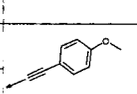
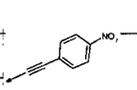
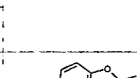
1261	rac	
1262	+	
1263	–	
1264	rac	
1265	+	
1266	–	
1267	rac	
1268	+	
1269	–	
1270	rac	
1271	+	
1272	–	
1273	rac	
1274	+	
1275	–	
1276	rac	
1277	+	
1278	–	
1279	rac	
1280	+	
1281	–	
1282	rac	
1283	+	
1284	–	
1285	rac	
1286	+	
1287	–	
1288	rac	
1289	+	
1290	–	

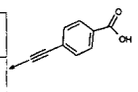
340

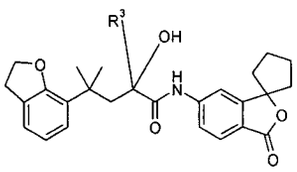
1291	rac	
1292	+	
1293	–	
1294	rac	
1295	+	
1296	–	
1297	rac	
1298	+	
1299	–	
1300	rac	
1301	+	
1302	–	
1303	rac	
1304	+	
1305	–	
1306	rac	
1307	+	
1308	–	
1309	rac	
1310	+	
1311	–	
1312	rac	
1313	+	
1314	–	
1315	rac	
1316	+	
1317	–	
1318	rac	
1319	+	
1320	–	

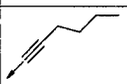
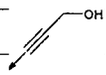
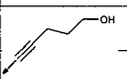
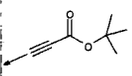


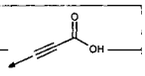
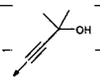
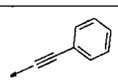
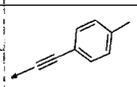
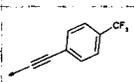
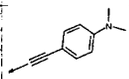
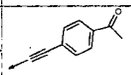
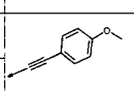
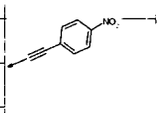
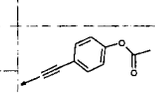
N.°	Racémico o enantiómero	R3
1321	rac	
1322	+	
1323	–	
1324	rac	
1325	+	
1326	–	
1327	rac	
1328	+	
1329	–	
1330	rac	
1331	+	
1332	–	
1333	rac	
1334	+	
1335	–	
1336	rac	
1337	+	
1338	–	
1339	rac	
1340	+	
1341	–	
1342	rac	
1343	+	
1344	–	
1345	rac	
1346	+	
1347	–	

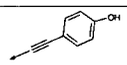
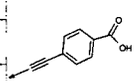
1348	rac	
1349	+	
1350	–	
1351	rac	
1352	+	
1353	–	
1354	rac	
1355	+	
1356	–	
1357	rac	
1358	+	
1359	–	
1360	rac	
1361	+	
1362	–	
1363	rac	
1364	+	
1365	–	
1366	rac	
1367	+	
1368	–	
1369	rac	
1370	+	
1371	–	
1372	rac	
1373	+	
1374	–	
1375	rac	
1376	+	
1377	–	

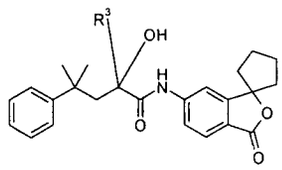
1378	rac	
1379	+	
1380	-	

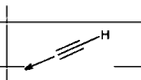
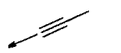
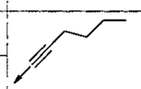
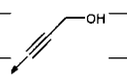
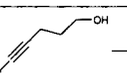
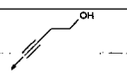


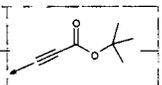
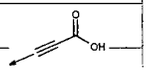
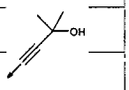
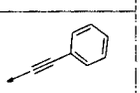
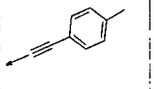
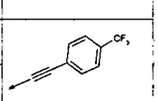
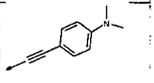
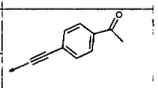
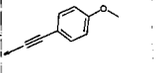
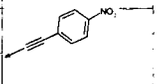
N.º	Racémico o enantiómero	R3
1381	rac	
1382	+	
1383	-	
1384	rac	
1385	+	
1386	-	
1387	rac	
1388	+	
1389	-	
1390	rac	
1391	+	
1392	-	
1393	rac	
1394	+	
1395	-	
1396	rac	
1397	+	
1398	-	
1399	rac	
1400	+	
1401	-	
1402	rac	
1403	+	
1404	-	

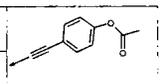
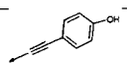
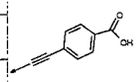
1405	rac	
1406	+	
1407	–	
1408	rac	
1409	+	
1410	–	
1411	rac	
1412	+	
1413	–	
1414	rac	
1415	+	
1416	–	
1417	rac	
1418	+	
1419	–	
1420	rac	
1421	+	
1422	–	
1423	rac	
1424	+	
1425	–	
1426	rac	
1427	+	
1428	–	
1429	rac	
1430	+	
1431	–	
1432	rac	
1433	+	
1434	–	

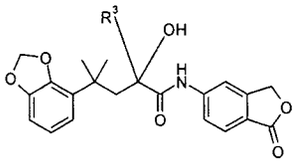
1435	rac	
1436	+	
1437	-	
1438	rac	
1439	+	
1440	-	

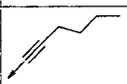
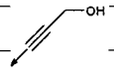
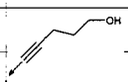


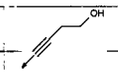
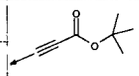
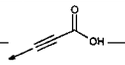
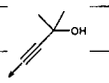
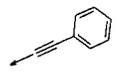
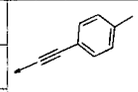
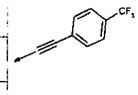
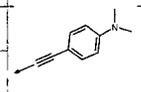
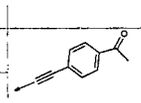
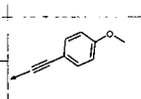
N.°	Racémico o enantiómero	R3
1441	rac	
1442	+	
1443	-	
1444	rac	
1445	+	
1446	-	
1447	rac	
1448	+	
1449	-	
1450	rac	
1451	+	
1452	-	
1453	rac	
1454	+	
1455	-	
1456	rac	
1457	+	
1458	-	
1459	rac	
1460	+	
1461	-	

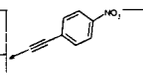
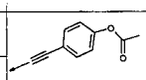
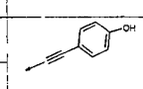
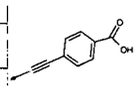
1462	rac	
1463	+	
1464	–	
1465	rac	
1466	+	
1467	–	
1468	rac	
1469	+	
1470	–	
1471	rac	
1472	+	
1473	–	
1474	rac	
1475	+	
1476	–	
1477	rac	
1478	+	
1479	–	
1480	rac	
1481	+	
1482	–	
1483	rac	
1484	+	
1485	–	
1486	rac	
1487	+	
1488	–	
1489	rac	
1490	+	
1491	–	

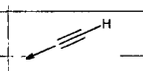
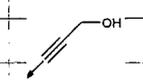
1492	rac	
1493	+	
1494	–	
1495	rac	
1496	+	
1497	–	
1498	rac	
1499	+	
1500	–	

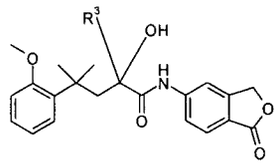


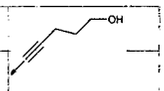
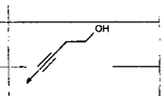
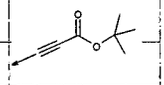
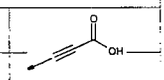
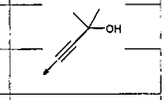
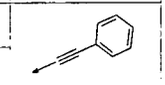
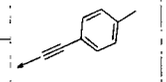
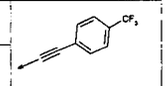
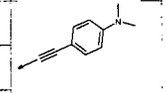
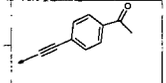
N.º	Racémico o enantiómero	R3
1501	rac	
1502	+	
1503	–	
1504	rac	
1505	+	
1506	–	
1507	rac	
1508	+	
1509	–	
1510	rac	
1511	+	
1512	–	
1513	rac	
1514	+	
1515	–	
1516	rac	
1517	+	
1518	–	

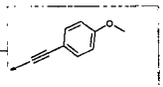
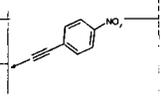
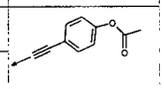
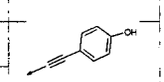
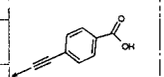
1519	rac	
1520	+	
1521	–	
1522	rac	
1523	+	
1524	–	
1525	rac	
1526	+	
1527	–	
1528	rac	
1529	+	
1530	–	
1531	rac	
1532	+	
1533	–	
1534	rac	
1535	+	
1536	–	
1537	rac	
1538	+	
1539	–	
1540	rac	
1541	+	
1542	–	
1543	rac	
1544	+	
1545	–	
1546	rac	
1547	+	
1548	–	

1549	rac	
1550	+	
1551	–	
1552	rac	
1553	+	
1554	–	
1555	rac	
1556	+	
1557	–	
1558	rac	
1559	+	
1560	–	

N.°	Racémico o enantiómero	R3
1561	rac	
1562	+	
1563	–	
1564	rac	
1565	+	
1566	–	
1567	rac	
1568	+	
1569	–	
1570	rac	
1571	+	
1572	–	
1573	rac	
1574	+	
1575	–	



1576	rac	
1577	+	
1578	–	
1579	rac	
1580	+	
1581	–	
1582	rac	
1583	+	
1584	–	
1585	rac	
1586	+	
1587	–	
1588	rac	
1589	+	
1590	–	
1591	rac	
1592	+	
1593	–	
1594	rac	
1595	+	
1596	–	
1597	rac	
1598	+	
1599	–	
1600	rac	
1601	+	
1602	–	
1603	rac	
1604	+	
1605	–	

1606	rac	
1607	+	
1608	-	
1609	rac	
1610	+	
1611	-	
1612	rac	
1613	+	
1614	-	
1615	rac	
1616	+	
1617	-	
1618	rac	
1619	+	
1620	-	

14. Composición farmacéutica que contiene al menos un compuesto de la fórmula general I de acuerdo con una de las reivindicaciones 1 a 13 y eventualmente al menos otro principio activo junto con vehículos y/o coadyuvantes compatibles con el uso farmacéutico.

15. Composición farmacéutica de acuerdo con la reivindicación 14 en la cual el ingrediente activo adicional es SERM (un modulador selectivo de receptor de estrógeno), un inhibidor de la aromatasa, un antiestrógeno o una prostaglandina.

16. Composición farmacéutica de acuerdo con la reivindicación 14 en la cual el ingrediente activo puede ser

tamoxifeno, 5-(4-{5-[(RS)-(4,4,5,5,5-pentafluoropentil)sulfinil]pentiloxi}fenil)-6-fenil-8,9-dihidro-7H-benzociclohepten-2-ol (documento WO 00/03979), ICI 182 780 (7alfa-[9-(4,4,5,5-pentafluoropentilsulfinil)nonil]estra-1,3,5(10)-trien-3,17-beta-diol), 11beta-fluoro-7alfa-[5-(metil{3-[(4,4,5,5,5-pentafluoropentil)sulfanil]-propil}amino)pentil]estra-1,3,5(10)-trien-3,17beta-diol (documento WO 98/07740), 11beta-fluoro-7alfa-{5-[metil(7,7,8,8,9,9,10,10,10-nonafluorodecil)amino]pentil}estra-1,3,5(10)-trien-3,17beta-diol (documento WO 99/33855), 11beta-fluoro-17alfa-metil-7alfa-{5-[metil-(8,8,9,9,9-pentafluorononil)amino]pentil}estra-1,3,5(10)-trien-3,17beta-diol (documento WO 03/045972), clomifeno, raloxifeno, así como otros compuestos de eficacia antiestrogénica, e inhibidores de la aromatasa tales como, p. ej., fadrozol, formestano, letrozol, anastrozol o atamestano.

17. Uso de compuestos de acuerdo con una de las reivindicaciones 1 a 13 para la preparación de un agente farmacéutico.

18. Uso de compuestos de acuerdo con la reivindicación 17 para la preparación de un agente farmacéutico para la prevención de enfermedades ginecológicas tales como endometriosis, leiomiomas de útero, hemorragias disfuncionales y dismenorrea.

19. Uso de compuestos de acuerdo con la reivindicación 17 para la preparación de un medicamento para la terapia y la prevención de tumores dependientes de hormonas.

20. Uso de compuestos de acuerdo con la reivindicación 17 para la preparación de un medicamento para la terapia y la prevención de carcinomas de mama.

21. Uso de compuestos de acuerdo con la reivindicación 17 para la preparación de un medicamento para la terapia y la prevención de carcinoma de endometrio.

22. Uso de compuestos de acuerdo con la reivindicación 17 para la preparación de un medicamento para la terapia y la prevención de carcinomas de ovario.

23. Uso de compuestos de acuerdo con la reivindicación 17 para la preparación de un medicamento para la terapia y la prevención de carcinomas de próstata.

24. Uso de compuestos de acuerdo con la reivindicación 17 para la preparación de un medicamento para la terapia de reemplazo hormonal femenina.

25. Uso de compuestos de acuerdo con la reivindicación 17 para el control de la fertilidad femenina

26. Proceso para la adición selectiva de compuestos litio alquinilo y magnesio haloalquinilo a la cetoamida.

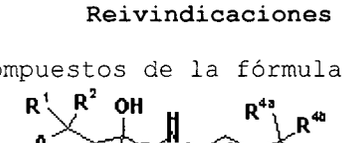
REIVINDICACIONES CON ENMIENDAS

Recibidas en la OFICINA internacional el 4 de octubre de 2006 (4/10/2006)

+ Declaración

Reivindicaciones

1. Compuestos de la fórmula general I



(I),

en donde

R^1 y R^2 son, de modo independiente entre sí, un átomo de hidrógeno, un grupo alquilo C_1-C_5 lineal o no lineal, ramificado o no ramificado, que además forma junto con el átomo de C de la cadena un anillo con un total de 3-7 miembros,

R^3 es un radical C≡C-R^a, en donde

R^a es un átomo de hidrógeno o un alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_{10}, heterocicloalquilo eventualmente mono- o polisustituido, igual o diferente, con K o un arilo o heteroarilo eventualmente mono- o polisustituido, igual o diferente, con L,

K es ciano, halógeno, hidroxi, nitro, -C(O)R^b, CO_2R^b, -O-R^b, -S-R^b, $SO_2NR^cR^d$, -C(O)-NR^cR^d, -OC(O)-NR^cR^d, -C=NOR^b -NR^cR^d o un cicloalquilo C_3-C_{10},

heterocicloalquilo eventualmente mono- o polisustituido, igual o diferente, con M o arilo o heteroarilo eventualmente mono- o polisustituido con L,

L es alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, perfluoroalquilo C_1-C_6, perfluoroalcoxi C_1-C_6, alcoxi C_1-C_6-alcoxi C_1-C_6, $(CH_2)_p$-cicloalquilo C_3-C_{10}, $(CH_2)_p$-heterocicloalquilo, $(CH_2)_pCN$, $(CH_2)_pHal$, $(CH_2)_pNO_2$, $(CH_2)_p$-arilo C_6-C_{12}, $(CH_2)_p$-heteroarilo,

$-(CH_2)_pPO_3(R^b)_2$,

$-(CH_2)_pNR^cR^d$, $-(CH_2)_pNR^eCOR^b$,

$-(CH_2)_pNR^eCSR^b$, $-(CH_2)_pNR^eS(O)R^b$,

$-(CH_2)_pNR^eS(O)_2R^b$,

$-(CH_2)_pNR^eCONR^cR^d$,

$-(CH_2)_pNR^eCOOR^b$,

$-(CH_2)_pNR^eC(NH)NR^cR^d$,

$-(CH_2)_pNR^eCSNR^cR^d$,

$-(CH_2)_pNR^eS(O)NR^cR^d$,

$-(CH_2)_pNR^eS(O)_2NR^cR^d$, $-(CH_2)_pCOR^b$,

$-(CH_2)_pCSR^b$, $-(CH_2)_pS(O)R^b$,

$-(CH_2)_pS(O)(NH)R^b$, $-(CH_2)_pS(O)_2R^b$,

$-(CH_2)_pS(O)_2NR^cR^d$, $-(CH_2)_pSO_2OR^b$,

$-(CH_2)_pCO_2R^b$, $-(CH_2)_pCONR^cR^d$,

$-(CH_2)_pCSNR^cR^d$, $-(CH_2)_pOR^b$,

$-(CH_2)_pSR^b$, $-(CH_2)_pCR^b(OH)-R^e$,

$-(CH_2)_p-C=NOR^b$, $-O-(CH_2)_n-O-$,

$-O-(CH_2)_n-CH_2-$, $-O-CH=CH-$ o

$-(CH_2)_{n+2}-$, en donde es n = 1 ó 2 y los átomos de oxígeno y/o átomos de carbono terminales están unidos con átomos de carbono del anillo directamente adyacentes,

M es alquilo C_1-C_6 o un grupo

$-COR^b$, CO_2R^b, $-O-R^b$ o $-NR^cR^d$, en donde

R^b es un átomo de hidrógeno o un alquilo C_1-C_6, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_{10}, arilo C_6-C_{12} o perfluoroalquilo C_1-C_3 y

R^c y R^d son, de modo independiente entre sí, un átomo de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_{10}, arilo C_6-C_{12}, $C(O)R^b$ o un grupo hidroxi, en donde cuando

R^c es un grupo hidroxi, R^d sólo puede ser un átomo de hidrógeno, un alquilo C_1-C_6, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_{10} o arilo C_6-C_{12} y viceversa, así como

R^e es un átomo de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_{10} o arilo C_6-C_{12} y

p puede ser una cifra de 0 a 6,

o

R^3 es un radical $C=C-R^gR^h$, en donde

R^g y R^h son, de modo independiente entre sí, un átomo de hidrógeno o un alquilo C_1-C_8, alquenilo C_2-C_8 o alquinilo C_2-C_8 eventualmente mono- o polisustituido, igual o diferente, con X, en donde

X es un ciano, halógeno, hidroxi, nitro, $-C(O)R^b$, CO_2R^b, $-O-R^b$, $-C(O)-NR^cR^d$, $-NR^cR^d$ con los significados ya mencionados más arriba para R^b, R^c y R^d y

R^{4a} y R^{4b} son, de modo independiente entre sí, un átomo de hidrógeno, un alquilo C_1-C_4, un alquenilo C_2-C_4 o forman, junto con el átomo de carbono del anillo, un anillo de 3-6 miembros,

A es un anillo aromático carbocíclico o heterocíclico mono- o bicíclico, que puede estar eventualmente mono- o polisustituido con alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, perfluoroalquilo C_1-C_6, perfluoroalcoxi C_1-C_6, alcoxi C_1-C_6-alquilo C_1-C_6, alcoxi C_1-C_6-alcoxi C_1-C_6, $(CH_2)_p$-cicloalquilo C_3-C_{10}, $(CH_2)_p$-

heterocicloalquilo, $(CH_2)_pCN$, $(CH_2)_pHal$, $(CH_2)_pNO_2$, $(CH_2)_p$-arilo C_6-C_{12}, $(CH_2)_p$-heteroarilo, $-(CH_2)_pPO_3(R^b)_2$, $-(CH_2)_pNR^cR^d$, $-(CH_2)_pNR^eCOR^b$, $-(CH_2)_pNR^eCSR^b$, $-(CH_2)_pNR^eS(O)R^b$, $-(CH_2)_pNR^eS(O)_2R^b$, $-(CH_2)_pNR^eCONR^cR^d$, $-(CH_2)_pNR^eCOOR^b$, $-(CH_2)_pNR^eC(NH)NR^cR^d$, $-(CH_2)_pNR^eCSNR^cR^d$, $-(CH_2)_pNR^eS(O)NR^cR^d$, $-(CH_2)_pNR^eS(O)_2NR^cR^d$, $-(CH_2)_pCOR^b$, $-(CH_2)_pCSR^b$, $-(CH_2)_p S(O)R^b$, $-(CH_2)_pS(O)(NH)R^b$, $-(CH_2)_pS(O)_2R^b$, $-(CH_2)_pS(O)_2NR^cR^d$, $-(CH_2)_pSO_2OR^b$, $-(CH_2)_pCO_2R^b$, $-(CH_2)_pCONR^cR^d$, $-(CH_2)_pCSNR^cR^d$, $-(CH_2)_pOR^b$, $-(CH_2)_pSR^b$, $-(CH_2)_pCR^b(OH)-R^d$, $-(CH_2)_p-C=NOR^b$, $-O-(CH_2)_n-O-$, $-O-(CH_2)_n-CH_2-$, $-O-CH=CH-$ o $-(CH_2)_{n+2}-$, en donde es n = 1 ó 2 y los átomos de oxígeno y/o átomos de carbono están unidos con átomos de carbono del anillo directamente adyacentes o

A es un radical $-CO_2R^b$, $C(O)NR^cR^d$, COR^b,

o

A es un grupo alquenilo $-CR^5=CR^6R^7$, en donde R^5, R^6 y R^7 son iguales o diferentes y, de modo independiente entre sí, son átomos de hidrógeno, átomos de halógeno, radicales arilo o un grupo alquilo C_1-C_5 no sustituido o parcial o totalmente fluorado o

A es un grupo alquinilo $-C\equiv CR^5$, con el significado indicado arriba para R^5 y

B es un grupo carbonilo o un grupo CH_2,

así como sus sales farmacéuticamente aceptables.

2. Compuestos de acuerdo con la reivindicación 1, en donde R^1 y R^2 son preferentemente un átomo de hidrógeno, un grupo metilo o etilo.

3. Compuestos de acuerdo con la reivindicación 1, en donde R^1 y R^2 forman con preferencia, junto con el átomo de C de la cadena, un anillo con un total de 3-7 miembros.

4. Compuestos de acuerdo con la reivindicación 1 a 3, en donde R^3 es preferentemente alquenilo, alquinilo, arilalquinilo, heteroarilalquinilo, cicloalquilalquinilo, heterocicloalquilalquinilo.

5. Compuestos de acuerdo con una de las reivindicaciones precedentes, en donde R^3 es preferentemente un grupo vinilo, etinilo, propinilo, butinilo, pentinilo, hexinilo, heptinilo, octinilo, hidroxipropinilo, hidroxibutinilo, 3-hidroxi-3-metilbutinilo, hidroxipentinilo, carboxipropinilo, t-butilcarboxipropinilo, feniletinilo, (hidroxifenil)etinilo, (metoxifenil)etinilo, (dimetilaminofenil)etinilo, (metilfenil)etinilo, (cianofenil)etinilo, (trifluorometil)etinilo, (difenil)etinilo, (nitrofenil)etinilo, (ter-butilfenil)etinilo, (acetilfenil)etinilo,

(acetoxifenil)etinilo, (carboxifenil)etinilo o benciletinilo.

6. Compuestos de acuerdo con una de las reivindicaciones precedentes, en donde A es preferentemente un anillo aromático.

7. Compuestos de acuerdo con una de las reivindicaciones precedentes, en donde A es preferentemente un radical fenilo o naftilo.

8. Compuestos de acuerdo con la reivindicación 7, en donde A es preferentemente un radical fenilo no sustituido o eventualmente mono- o polisustituido.

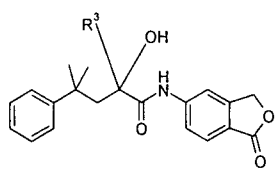
9. Compuestos de acuerdo con la reivindicación 8, en donde el radical fenilo está sustituido preferentemente con uno o dos átomos de halógeno o un grupo trifluorometilo.

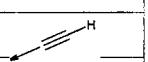
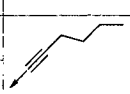
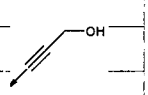
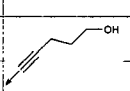
10. Compuestos de acuerdo con la reivindicación 9, en donde los átomos de halógeno son preferentemente cloro y/o flúor.

11. Compuestos de acuerdo con las reivindicaciones 1-8, en donde A es preferentemente un anillo fenilo sustituido con $-O-(CH_2)_n-O-$ u $-O-(CH_2)_n-CH_2-$, en donde los átomos de carbono del anillo directamente adyacentes están unidos.

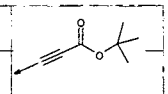
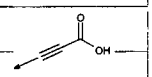
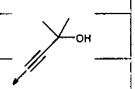
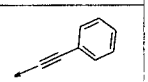
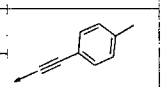
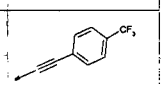
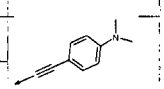
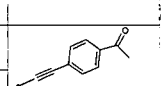
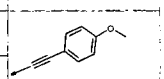
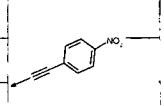
12. Compuestos de acuerdo con una de las reivindicaciones precedentes, en donde R^{4a} y R^{4b} son en cada caso, de modo independiente entre sí, un átomo de hidrógeno.

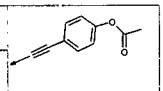
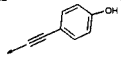
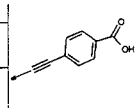
13. Compuestos de acuerdo con la reivindicación 1 a 12, a saber

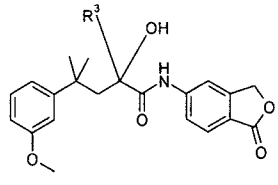


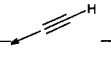
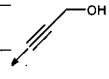
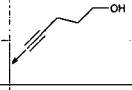
N.°	Racémico o enantiómero	R3
1	rac	
2	+	
3	–	
4	rac	
5	+	
6	–	
7	rac	
8	+	
9	–	
10	rac	
11	+	
12	–	
13	rac	
14	+	
15	–	
16	rac	
17	+	
18	–	
19	rac	
20	+	
21	–	

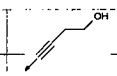
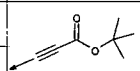
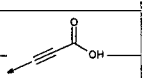
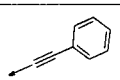
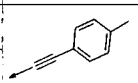
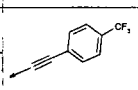
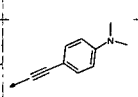
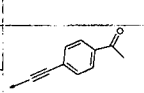
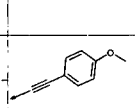
360

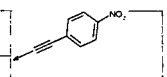
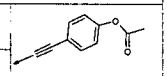
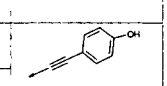
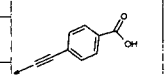
22	rac	
23	+	
24	–	
25	rac	
26	+	
27	–	
28	rac	
29	+	
30	–	
31	rac	
32	+	
33	–	
34	rac	
35	+	
36	–	
37	rac	
38	+	
39	–	
40	rac	
41	+	
42	–	
43	rac	
44	+	
45	–	
46	rac	
47	+	
48	–	
49	rac	
50	+	
51	–	

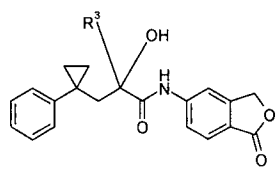
52	rac	
53	+	
54	–	
55	rac	
56	+	
57	–	
58	rac	
59	+	
60	–	

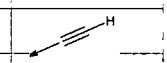
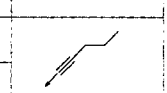
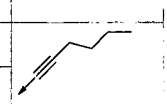
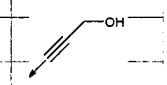


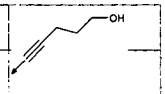
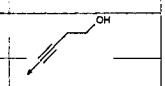
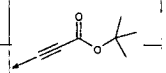
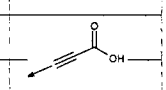
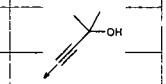
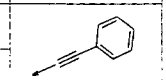
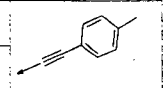
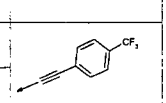
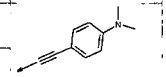
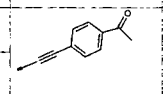
N.°	Racémico o enantiómero	R3
61	rac	
62	+	
63	–	
64	rac	
65	+	
66	–	
67	rac	
68	+	
69	–	
70	rac	
71	+	
72	–	
73	rac	
74	+	
75	–	
76	rac	
77	+	
78	–	

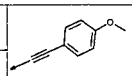
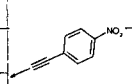
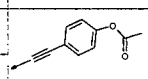
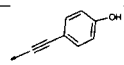
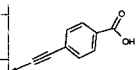
79	rac	
80	+	
81	–	
82	rac	
83	+	
84	–	
85	rac	
86	+	
87	–	
88	rac	
89	+	
90	–	
91	rac	
92	+	
93	–	
94	rac	
95	+	
96	–	
97	rac	
98	+	
99	–	
100	rac	
101	+	
102	–	
103	rac	
104	+	
105	–	
106	rac	
107	+	
108	–	

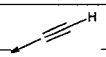
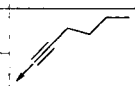
109	rac	
110	+	
111	–	
112	rac	
113	+	
114	–	
115	rac	
116	+	
117	–	
118	rac	
119	+	
120	–	

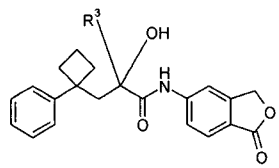


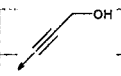
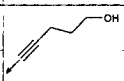
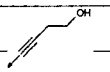
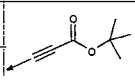
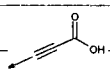
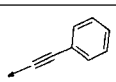
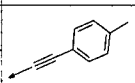
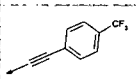
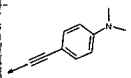
N.°	Racémico o enantiómero	R3
121	rac	
122	+	
123	–	
124	rac	
125	+	
126	–	
127	rac	
128	+	
129	–	
130	rac	
131	+	
132	–	
133	rac	
134	+	
135	–	

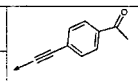
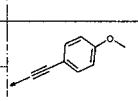
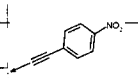
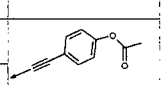
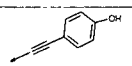
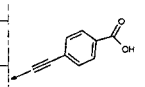
136	rac	
137	+	
138	–	
139	rac	
140	+	
141	–	
142	rac	
143	+	
144	–	
145	rac	
146	+	
147	–	
148	rac	
149	+	
150	–	
151	rac	
152	+	
153	–	
154	rac	
155	+	
156	–	
157	rac	
158	+	
159	–	
160	rac	
161	+	
162	–	
163	rac	
164	+	
165	–	

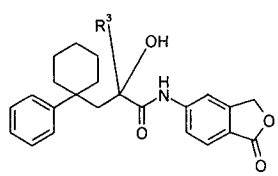
166	rac	
167	+	
168	–	
169	rac	
170	+	
171	–	
172	rac	
173	+	
174	–	
175	rac	
176	+	
177	–	
178	rac	
179	+	
180	–	

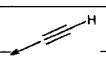
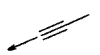
N.º	Racémico o enantiómero	R3
181	rac	
182	+	
183	–	
184	rac	
185	+	
186	–	
187	rac	
188	+	
189	–	
190	rac	
191	+	
192	–	

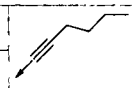
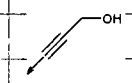
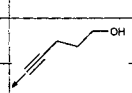
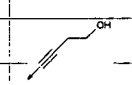
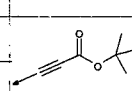
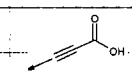
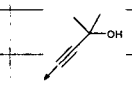
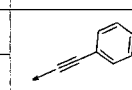
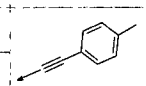
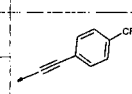


193	rac	
194	+	
195	–	
196	rac	
197	+	
198	–	
199	rac	
200	+	
201	–	
202	rac	
203	+	
204	–	
205	rac	
206	+	
207	–	
208	rac	
209	+	
210	–	
211	rac	
212	+	
213	–	
214	rac	
215	+	
216	–	
217	rac	
218	+	
219	–	
220	rac	
221	+	
222	–	

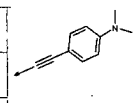
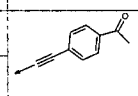
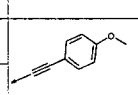
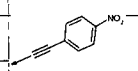
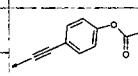
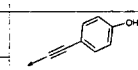
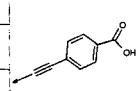
223	rac	
224	+	
225	–	
226	rac	
227	+	
228	–	
229	rac	
230	+	
231	–	
232	rac	
233	+	
234	–	
235	rac	
236	+	
237	–	
238	rac	
239	+	
240	–	

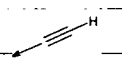
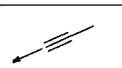


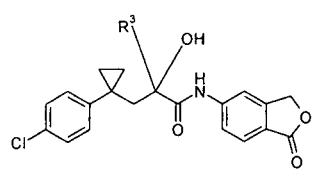
N.º	Racémico o enantiómero	R3
241	rac	
242	+	
243	–	
244	rac	
245	+	
246	–	
247	rac	
248	+	
249	–	

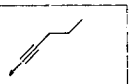
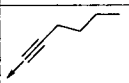
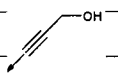
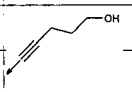
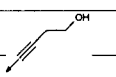
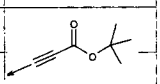
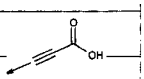
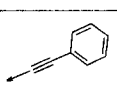
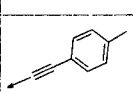
250	rac	
251	+	
252	–	
253	rac	
254	+	
255	–	
256	rac	
257	+	
258	–	
259	rac	
260	+	
261	–	
262	rac	
263	+	
264	–	
265	rac	
266	+	
267	–	
268	rac	
269	+	
270	–	
271	rac	
272	+	
273	–	
274	rac	
275	+	
276	–	
277	rac	
278	+	
279	–	

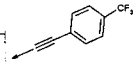
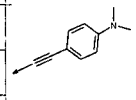
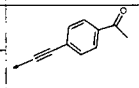
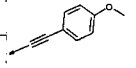
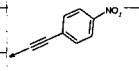
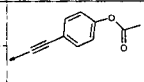
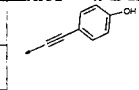
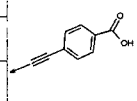
320

280	rac	
281	+	
282	–	
283	rac	
284	+	
285	–	
286	rac	
287	+	
288	–	
289	rac	
290	+	
291	–	
292	rac	
293	+	
294	–	
295	rac	
296	+	
297	–	
298	rac	
299	+	
300	–	

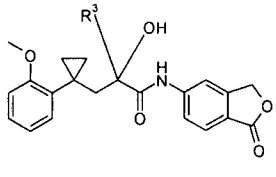
N.°	Racémico o enantiómero	R3
301	rac	
302	+	
303	–	
304	rac	
305	+	
306	–	

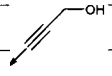
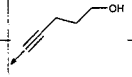
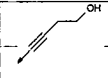
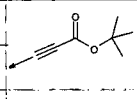
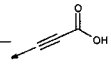
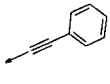


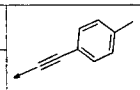
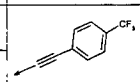
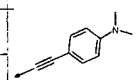
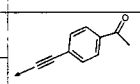
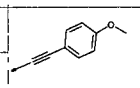
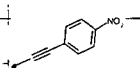
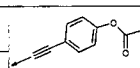
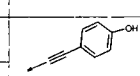
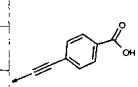
307	rac	
308	+	
309	–	
310	rac	
311	+	
312	–	
313	rac	
314	+	
315	–	
316	rac	
317	+	
318	–	
319	rac	
320	+	
321	–	
322	rac	
323	+	
324	–	
325	rac	
326	+	
327	–	
328	rac	
329	+	
330	–	
331	rac	
332	+	
333	–	
334	rac	
335	+	
336	–	

337	rac	
338	+	
339	–	
340	rac	
341	+	
342	–	
343	rac	
344	+	
345	–	
346	rac	
347	+	
348	–	
349	rac	
350	+	
351	–	
352	rac	
353	+	
354	–	
355	rac	
356	+	
357	–	
358	rac	
359	+	
360	–	

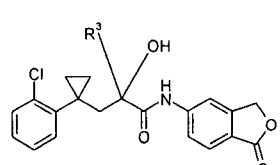
N.°	Racémico o enantiómero	R3
361	rac	
362	+	
363	–	

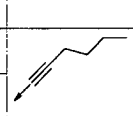
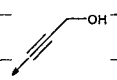
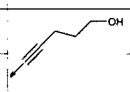
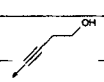
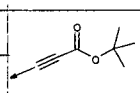
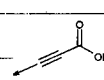


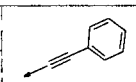
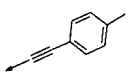
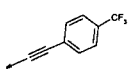
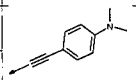
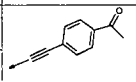
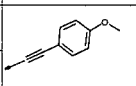
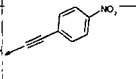
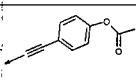
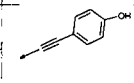
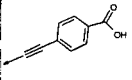
364	rac	
365	+	
366	–	
367	rac	
368	+	
369	–	
370	rac	
371	+	
372	–	
373	rac	
374	+	
375	–	
376	rac	
377	+	
378	–	
379	rac	
380	+	
381	–	
382	rac	
383	+	
384	–	
385	rac	
386	+	
387	–	
388	rac	
389	+	
390	–	
391	rac	
392	+	
393	–	

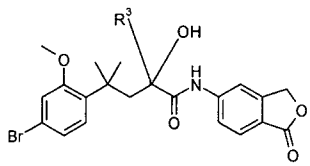
394	rac	
395	+	
396	-	
397	rac	
398	+	
399	-	
400	rac	
401	+	
402	-	
403	rac	
404	+	
405	-	
406	rac	
407	+	
408	-	
409	rac	
410	+	
411	-	
412	rac	
413	+	
414	-	
415	rac	
416	+	
417	-	
418	rac	
419	+	
420	-	

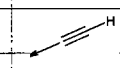
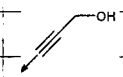
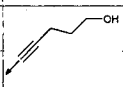
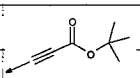
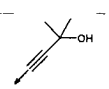
N.°	Racémico o enantiómero	R3

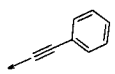
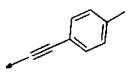
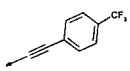
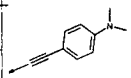
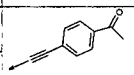
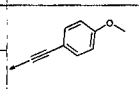
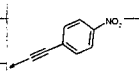
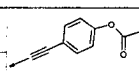
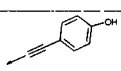
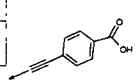


421	rac	
422	+	
423	–	
424	rac	
425	+	
426	–	
427	rac	
428	+	
429	–	
430	rac	
431	+	
432	–	
433	rac	
434	+	
435	–	
436	rac	
437	+	
438	–	
439	rac	
440	+	
441	–	
442	rac	
443	+	
444	–	
445	rac	
446	+	
447	–	
448	rac	
449	+	
450	–	

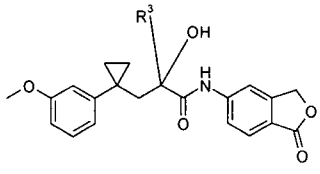
451	rac	
452	+	
453	–	
454	rac	
455	+	
456	–	
457	rac	
458	+	
459	–	
460	rac	
461	+	
462	–	
463	rac	
464	+	
465	–	
466	rac	
467	+	
468	–	
469	rac	
470	+	
471	–	
472	rac	
473	+	
474	–	
475	rac	
476	+	
477	–	
478	rac	
479	+	
480	–	

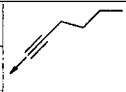
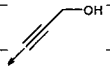
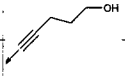
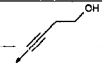
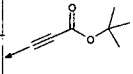
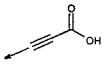


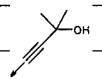
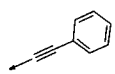
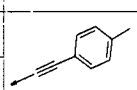
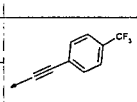
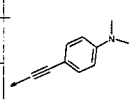
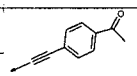
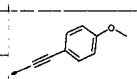
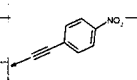
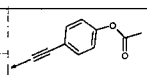
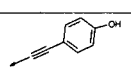
N.º	Racémico o enantiómero	R3
481	rac	
482	+	
483	–	
484	rac	
485	+	
486	–	
487	rac	
488	+	
489	–	
490	rac	
491	+	
492	–	
493	rac	
494	+	
495	–	
496	rac	
497	+	
498	–	
499	rac	
500	+	
501	–	
502	rac	
503	+	
504	–	
505	rac	
506	+	
507	–	
508	rac	

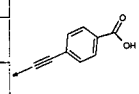
509	+	
510	–	
511	rac	
512	+	
513	–	
214	rac	
515	+	
516	–	
517	rac	
518	+	
519	–	
520	rac	
521	+	
522	–	
523	rac	
524	+	
525	–	
526	rac	
227	+	
528	–	
529	rac	
530	+	
531	–	
532	rac	
533	+	
534	–	
535	rac	
536	+	
537	–	
538	rac	

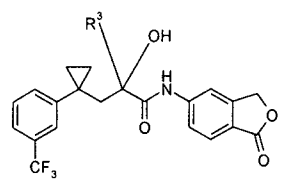
539	+
540	–

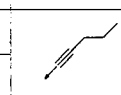
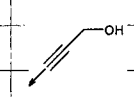
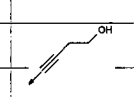
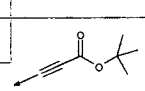


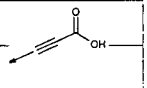
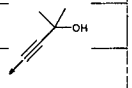
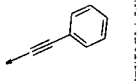
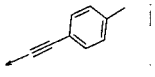
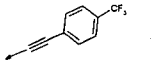
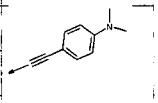
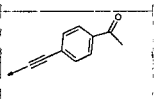
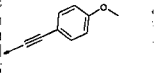
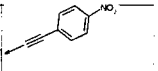
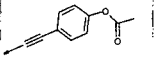
N.º	Racémico o enantiómero	R3
541	rac	
542	+	
543	–	
544	rac	
545	+	
546	–	
547	rac	
548	+	
549	–	
550	rac	
551	+	
552	–	
553	rac	
554	+	
555	–	
556	rac	
557	+	
558	–	
559	rac	
560	+	
561	–	
562	rac	
563	+	
564	–	
565	rac	

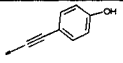
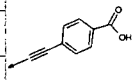
566	+	
567	–	
568	rac	
569	+	
570	–	
571	rac	
572	+	
573	–	
574	rac	
575	+	
576	–	
577	rac	
578	+	
579	–	
580	rac	
581	+	
582	–	
583	rac	
584	+	
585	–	
586	rac	
587	+	
588	–	
589	rac	
590	+	
591	–	
592	rac	
593	+	
594	–	
595	rac	

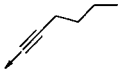
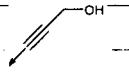
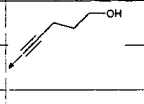
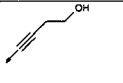
596	+	
597	-	
598	rac	
599	+	
600	-	

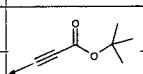
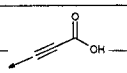
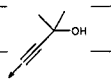
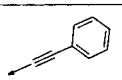
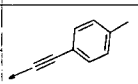
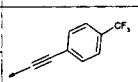
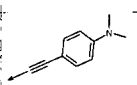
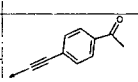
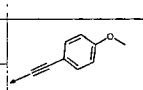
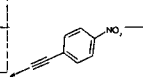


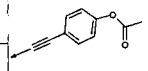
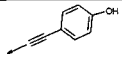
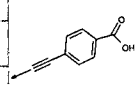
N.°	Racémico o enantiómero	R3
601	rac	
602	+	
603	-	
604	rac	
605	+	
606	-	
607	rac	
608	+	
609	-	
610	rac	
611	+	
612	-	
613	rac	
614	+	
615	-	
616	rac	
617	+	
618	-	
619	rac	
620	+	
621	-	
622	rac	

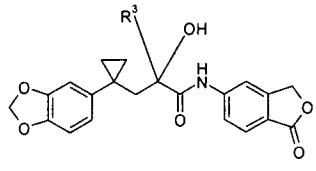
623	+	
624	–	
625	rac	
626	+	
627	–	
628	rac	
629	+	
630	–	
631	rac	
632	+	
633	–	
634	rac	
635	+	
636	–	
637	rac	
638	+	
639	–	
640	rac	
641	+	
642	–	
643	rac	
644	+	
645	–	
646	rac	
647	+	
648	–	
649	rac	
650	+	
651	–	
652	rac	

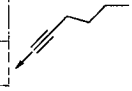
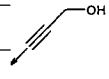
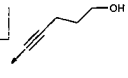
653	+	
654	–	
655	rac	
656	+	
657	–	
658	rac	
659	+	
660	–	

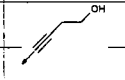
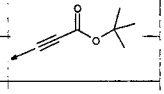
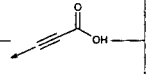
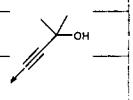
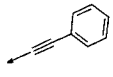
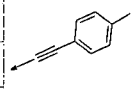
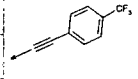
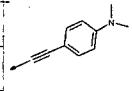
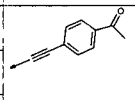
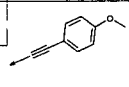
N.°	Racémico o enantiómero	R3
661	rac	
662	+	
663	–	
664	rac	
665	+	
666	–	
667	rac	
668	+	
669	–	
670	rac	
671	+	
672	–	
673	rac	
674	+	
675	–	
676	rac	
677	+	
678	–	
679	rac	

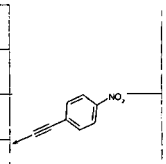
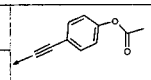
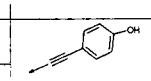
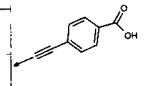
680	+	
681	–	
682	rac	
683	+	
684	–	
685	rac	
686	+	
687	–	
688	rac	
689	+	
690	–	
691	rac	
692	+	
693	–	
694	rac	
695	+	
696	–	
697	rac	
698	+	
699	–	
700	rac	
701	+	
702	–	
703	rac	
704	+	
705	–	
706	rac	
707	+	
708	–	
709	rac	

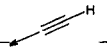
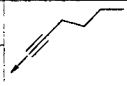
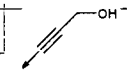
710	+	
711	–	
712	rac	
713	+	
714	–	
715	rac	
716	+	
717	–	
718	rac	
719	+	
720	–	

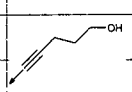
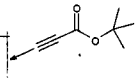
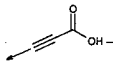
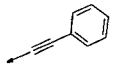
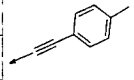
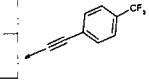
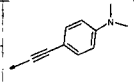
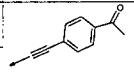


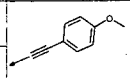
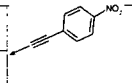
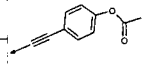
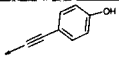
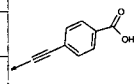
N.°	Racémico o enantiómero	R3
721	rac	
722	+	
723	–	
724	rac	
725	+	
726	–	
727	rac	
728	+	
729	–	
730	rac	
731	+	
732	–	
733	rac	
734	+	
735	–	
736	rac	

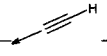
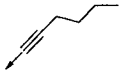
737	+	
738	–	
739	rac	
740	+	
741	–	
742	rac	
743	+	
744	–	
745	rac	
746	+	
747	–	
748	rac	
749	+	
750	–	
751	rac	
752	+	
753	–	
754	rac	
755	+	
756	–	
757	rac	
758	+	
759	–	
760	rac	
761	+	
762	–	
763	rac	
764	+	
765	–	
766	rac	

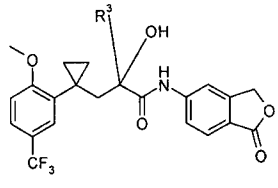
767	+	
768	–	
769	rac	
770	+	
771	–	
772	rac	
773	+	
774	–	
775	rac	
776	+	
777	–	
778	rac	
779	+	
780	–	

N.º	Racémico o enantiómero	R3
781	rac	
782	+	
783	–	
784	rac	
785	+	
786	–	
787	rac	
788	+	
789	–	
790	rac	
791	+	
792	–	
793	rac	

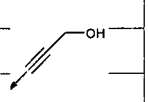
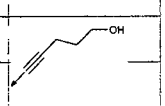
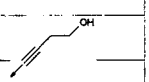
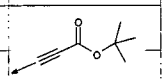
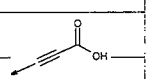
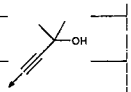
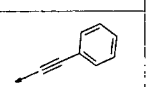
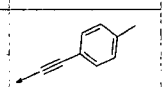
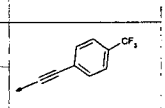
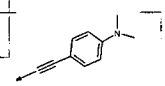
794	+	
795	–	
796	rac	
797	+	
798	–	
799	rac	
800	+	
801	–	
802	rac	
803	+	
804	–	
805	rac	
806	+	
807	–	
808	rac	
809	+	
810	–	
811	rac	
812	+	
813	–	
814	rac	
815	+	
816	–	
817	rac	
818	+	
819	–	
820	rac	
821	+	
822	–	
823	rac	

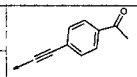
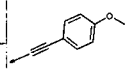
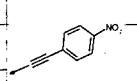
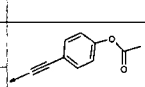
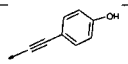
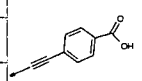
824	+	
825	-	
826	rac	
827	+	
828	-	
829	rac	
830	+	
831	-	
832	rac	
833	+	
834	-	
835	rac	
836	+	
837	-	
838	rac	
839	+	
840	-	

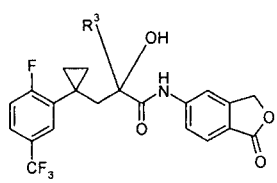
N.º	Racémico o enantiómero	R3
841	rac	
842	+	
843	-	
844	rac	
845	+	
846	-	
847	rac	
848	+	
849	-	
850	rac	

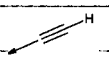


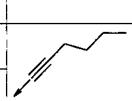
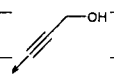
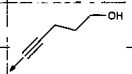
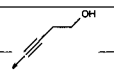
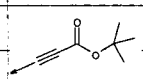
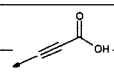
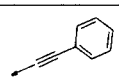
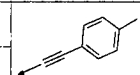
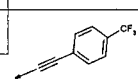
390

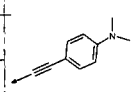
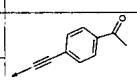
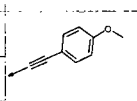
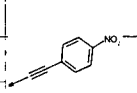
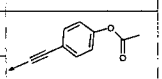
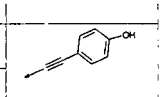
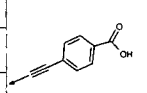
851	+	
852	-	
853	rac	
854	+	
855	-	
856	rac	
857	+	
858	-	
859	rac	
860	+	
861	-	
862	rac	
863	+	
864	-	
865	rac	
866	+	
867	-	
868	rac	
869	+	
870	-	
871	rac	
872	+	
873	-	
874	rac	
875	+	
876	-	
877	rac	
878	+	
879	-	
880	rac	

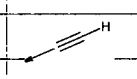
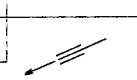
881	+	
882	–	
883	rac	
884	+	
885	–	
886	rac	
887	+	
888	–	
889	rac	
890	+	
891	–	
892	rac	
893	+	
894	–	
895	rac	
896	+	
897	–	
898	rac	
899	+	
900	–	

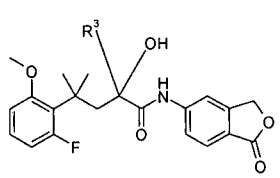


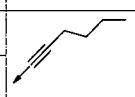
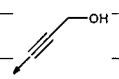
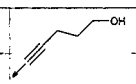
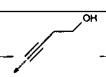
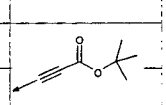
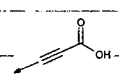
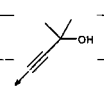
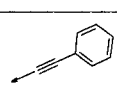
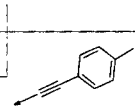
N.°	Racémico o enantiómero	R3
901	rac	
902	+	
903	–	
904	rac	
905	+	
906	–	
907	rac	

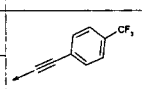
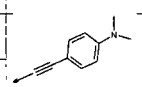
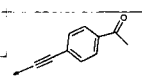
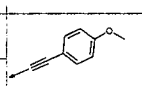
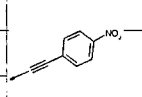
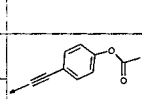
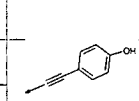
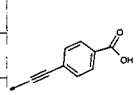
908	+	
909	-	
910	rac	
911	+	
912	-	
913	rac	
914	+	
915	-	
916	rac	
917	+	
918	-	
919	rac	
920	+	
921	-	
922	rac	
923	+	
924	-	
925	rac	
926	+	
927	-	
928	rac	
929	+	
930	-	
931	rac	
932	+	
933	-	
934	rac	
935	+	
936	-	
937	rac	

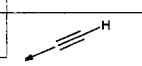
938	+	
939	–	
940	rac	
941	+	
942	–	
943	rac	
944	+	
945	–	
946	rac	
947	+	
948	–	
949	rac	
950	+	
951	–	
952	rac	
953	+	
954	–	
955	rac	
956	+	
957	–	
958	rac	
959	+	
960	–	

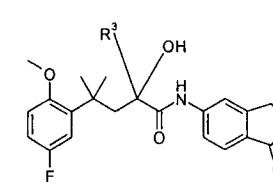
N.°	Racémico o enantiómero	R3
961	rac	
962	+	
963	–	
964	rac	

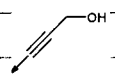
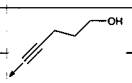
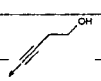
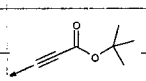
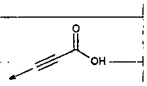
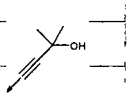
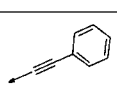


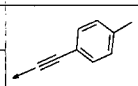
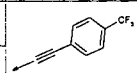
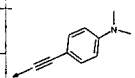
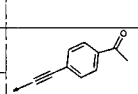
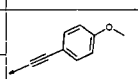
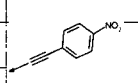
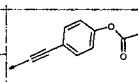
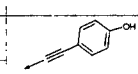
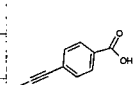
965	+	
966	-	
967	rac	
968	+	
969	-	
970	rac	
971	+	
972	-	
973	rac	
974	+	
975	-	
976	rac	
977	+	
978	-	
979	rac	
980	+	
981	-	
982	rac	
983	+	
984	-	
985	rac	
986	+	
987	-	
988	rac	
989	+	
990	-	
991	rac	
992	+	
993	-	
994	rac	

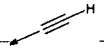
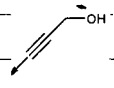
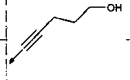
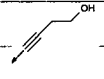
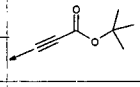
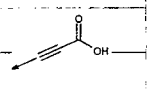
995	+	
996	-	
997	rac	
998	+	
999	-	
1000	rac	
1001	+	
1002	-	
1003	rac	
1004	+	
1005	-	
1006	rac	
1007	+	
1008	-	
1009	rac	
1010	+	
1011	-	
1012	rac	
1013	+	
1014	-	
1015	rac	
1016	+	
1017	-	
1018	rac	
1019	+	
1020	-	

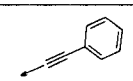
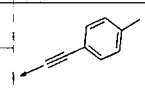
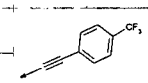
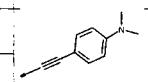
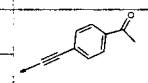
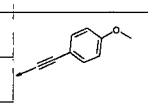
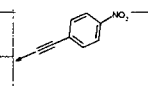
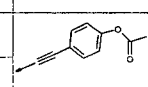
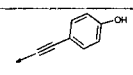
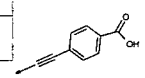
N.°	Racémico o enantiómero	R3
1021	rac	



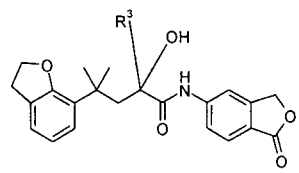
1022	+	
1023	–	
1024	rac	
1025	+	
1026	–	
1027	rac	
1028	+	
1029	–	
1030	rac	
1031	+	
1032	–	
1033	rac	
1034	+	
1035	–	
1036	rac	
1037	+	
1038	–	
1039	rac	
1040	+	
1041	–	
1042	rac	
1043	+	
1044	–	
1045	rac	
1046	+	
1047	–	
1048	rac	
1049	+	
1050	–	
1051	rac	

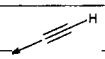
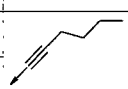
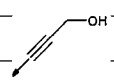
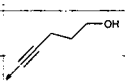
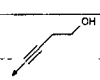
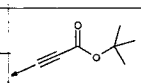
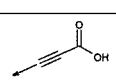
1052	+	
1053	-	
1054	rac	
1055	+	
1056	-	
1057	rac	
1058	+	
1059	-	
1060	rac	
1061	+	
1062	-	
1063	rac	
1064	+	
1065	-	
1066	rac	
1067	+	
1068	-	
1069	rac	
1070	+	
1071	-	
1072	rac	
1073	+	
1074	-	
1075	rac	
1076	+	
1077	-	
1078	rac	
1079	+	
1080	-	

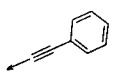
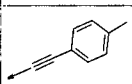
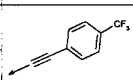
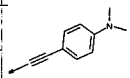
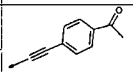
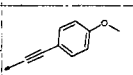
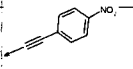
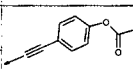
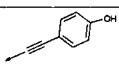
N.º	Racémico o enantiómero	R3
1081	rac	
1082	+	
1083	-	
1084	rac	
1085	+	
1086	-	
1087	rac	
1088	+	
1089	-	
1090	rac	
1091	+	
1092	-	
1093	rac	
1094	+	
1095	-	
1096	rac	
1097	+	
1098	-	
1099	rac	
1100	+	
1101	-	
1102	rac	
1103	+	
1104	-	
1105	rac	
1106	+	
1107	-	
1108	rac	

1109	+	
1110	–	
1111	rac	
1112	+	
1113	–	
1114	rac	
1115	+	
1116	–	
1117	rac	
1118	+	
1119	–	
1120	rac	
1121	+	
1122	–	
1123	rac	
1124	+	
1125	–	
1126	rac	
1127	+	
1128	–	
1129	rac	
1130	+	
1131	–	
1132	rac	
1133	+	
1134	–	
1135	rac	
1136	+	
1137	–	
1138	rac	

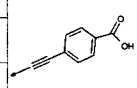
1139	+
1140	-

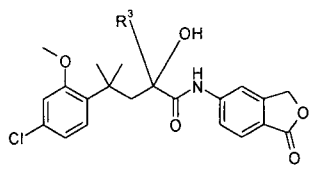


N.°	Racémico o enantiómero	R3
1141	rac	
1142	+	
1143	-	
1144	rac	
1145	+	
1146	-	
1147	rac	
1148	+	
1149	-	
1150	rac	
1151	+	
1152	-	
1153	rac	
1154	+	
1155	-	
1156	rac	
1157	+	
1158	-	
1159	rac	
1160	+	
1161	-	
1162	rac	
1163	+	
1164	-	
1165	rac	

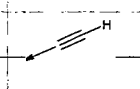
1166	+	
1167	-	
1168	rac	
1169	+	
1170	-	
1171	rac	
1172	+	
1173	-	
1174	rac	
1175	+	
1176	-	
1177	rac	
1178	+	
1179	-	
1180	rac	
1181	+	
1182	-	
1183	rac	
1184	+	
1185	-	
1186	rac	
1187	+	
1188	-	
1189	rac	
1190	+	
1191	-	
1192	rac	
1193	+	
1194	-	
1195	rac	

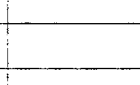
1196	+
1197	–
1198	rac
1199	+
1200	–





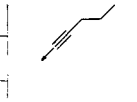
N.°	Racémico o enantiómero	R3
1201	rac	
1202	+	
1203	–	
1204	rac	
1205	+	
1206	–	
1207	rac	
1208	+	
1209	–	
1210	rac	
1211	+	
1212	–	
1213	rac	
1214	+	
1215	–	
1216	rac	
1217	+	
1218	–	
1219	rac	
1220	+	
1221	–	
1222	rac	





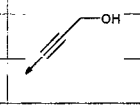


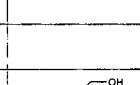


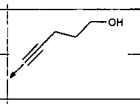


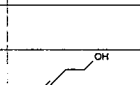




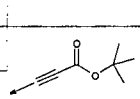


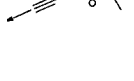


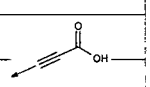
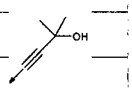
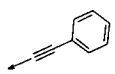
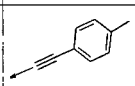
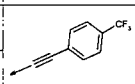
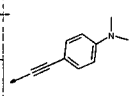
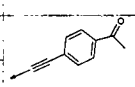
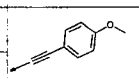
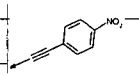
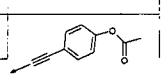


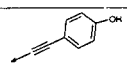
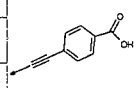
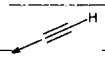
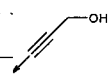
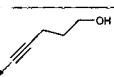
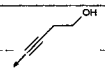


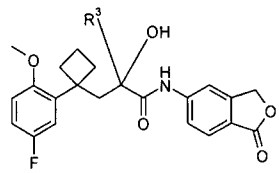


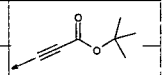
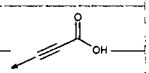
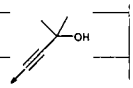
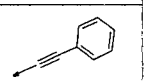
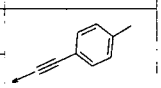
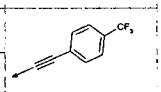
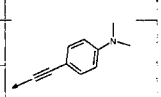
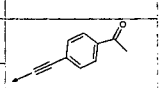
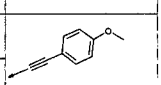
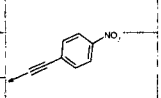


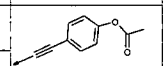
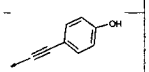
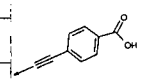


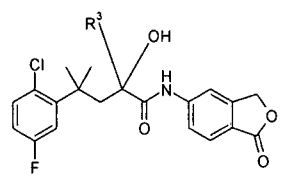
1223	+	
1224	–	
1225	rac	
1226	+	
1227	–	
1228	rac	
1229	+	
1230	–	
1231	rac	
1232	+	
1233	–	
1234	rac	
1235	+	
1236	–	
1237	rac	
1238	+	
1239	–	
1240	rac	
1241	+	
1242	–	
1243	rac	
1244	+	
1245	–	
1246	rac	
1247	+	
1248	–	
1249	rac	
1250	+	
1251	–	
1252	rac	

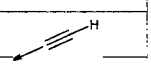
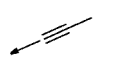
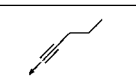
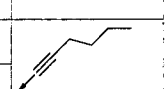
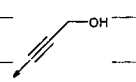
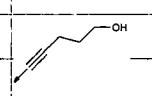
1253	+	
1254	–	
1255	rac	
1256	+	
1257	–	
1258	rac	
1259	+	
1260	–	
N.°	Racémico o enantiómero	R3
1261	rac	
1262	+	
1263	–	
1264	rac	
1265	+	
1266	–	
1267	rac	
1268	+	
1269	–	
1270	rac	
1271	+	
1272	–	
1273	rac	
1274	+	
1275	–	
1276	rac	
1277	+	
1278	–	
1279	rac	
1280	+	



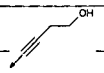
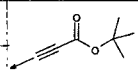
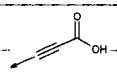
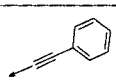
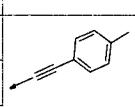
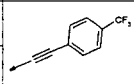
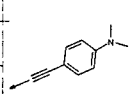
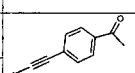
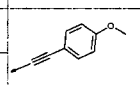
1281	-	
1282	rac	
1283	+	
1284	-	
1285	rac	
1286	+	
1287	-	
1288	rac	
1289	+	
1290	-	
1291	rac	
1292	+	
1293	-	
1294	rac	
1295	+	
1296	-	
1297	rac	
1298	+	
1299	-	
1300	rac	
1301	+	
1302	-	
1303	rac	
1304	+	
1305	-	
1306	rac	
1307	+	
1308	-	
1309	rac	
1310	+	

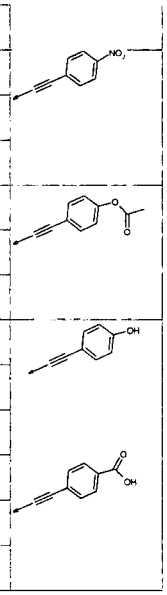
1311	-	
1312	rac	
1313	+	
1314	-	
1315	rac	
1316	+	
1317	-	
1318	rac	
1319	+	
1320	-	

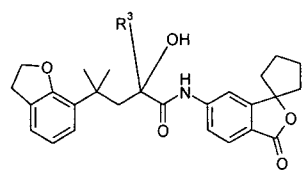


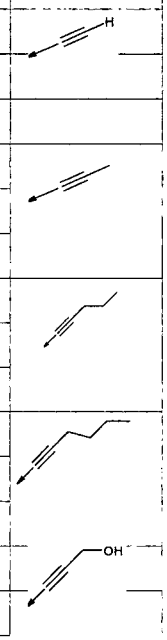
N.°	Racémico o enantiómero	R3
1321	rac	
1322	+	
1323	-	
1324	rac	
1325	+	
1326	-	
1327	rac	
1328	+	
1329	-	
1330	rac	
1331	+	
1332	-	
1333	rac	
1334	+	
1335	-	
1336	rac	
1337	+	

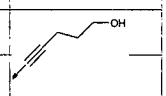
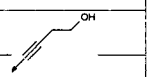
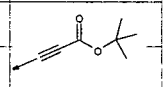
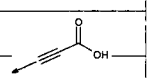
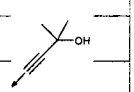
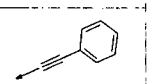
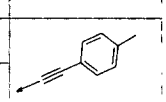
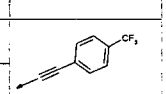
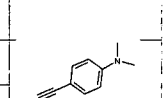
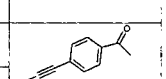
410

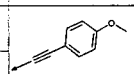
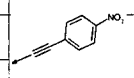
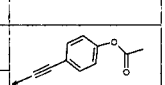
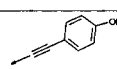
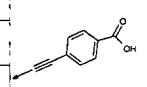
1338	-	
1339	rac	
1340	+	
1341	-	
1342	rac	
1343	+	
1344	-	
1345	rac	
1346	+	
1347	-	
1348	rac	
1349	+	
1350	-	
1351	rac	
1352	+	
1353	-	
1354	rac	
1355	+	
1356	-	
1357	rac	
1358	+	
1359	-	
1360	rac	
1361	+	
1362	-	
1363	rac	
1364	+	
1365	-	
1366	rac	
1367	+	

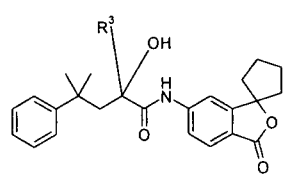
1368	-	
1369	rac	
1370	+	
1371	-	
1372	rac	
1373	+	
1374	-	
1375	rac	
1376	+	
1377	-	
1378	rac	
1379	+	
1380	-	

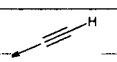
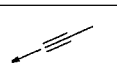
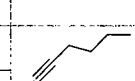


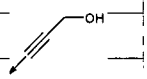
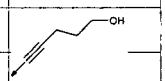
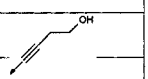
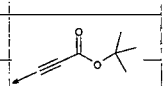
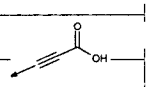
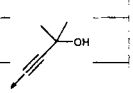
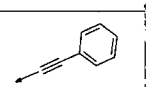
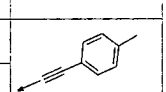
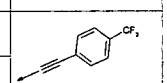
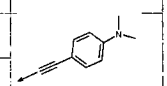
N.º	Racémico o enantiómero	R3
1381	rac	
1382	+	
1383	-	
1384	rac	
1385	+	
1386	-	
1387	rac	
1388	+	
1389	-	
1390	rac	
1391	+	
1392	-	
1393	rac	
1394	+	

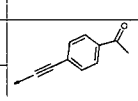
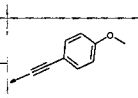
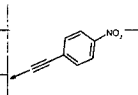
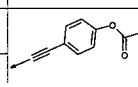
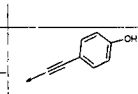
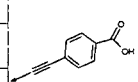
1395	–	
1396	rac	
1397	+	
1398	–	
1399	rac	
1400	+	
1401	–	
1402	rac	
1403	+	
1404	–	
1405	rac	
1406	+	
1407	–	
1408	rac	
1409	+	
1410	–	
1411	rac	
1412	+	
1413	–	
1414	rac	
1415	+	
1416	–	
1417	rac	
1418	+	
1419	–	
1420	rac	
1421	+	
1422	–	
1423	rac	
1424	+	

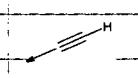
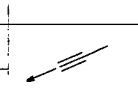
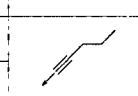
1425	–	
1426	rac	
1427	+	
1428	–	
1429	rac	
1430	+	
1431	–	
1432	rac	
1433	+	
1434	–	
1435	rac	
1436	+	
1437	–	
1438	rac	
1439	+	
1440	–	

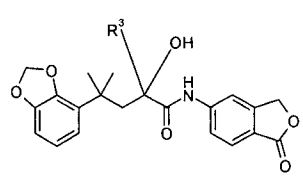


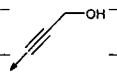
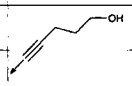
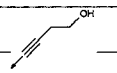
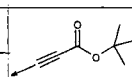
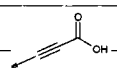
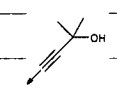
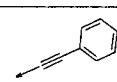
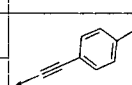
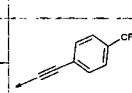
N.°	Racémico o enantiómero	R3
1441	rac	
1442	+	
1443	–	
1444	rac	
1445	+	
1446	–	
1447	rac	
1448	+	
1449	–	
1450	rac	
1451	+	

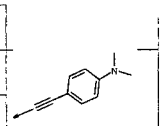
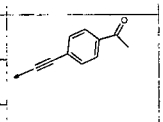
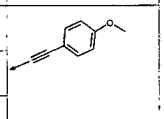
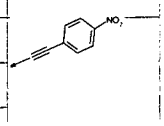
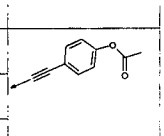
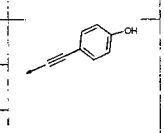
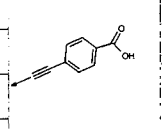
1452	–	
1453	rac	
1454	+	
1455	–	
1456	rac	
1457	+	
1458	–	
1459	rac	
1460	+	
1461	–	
1462	rac	
1463	+	
1464	–	
1465	rac	
1466	+	
1467	–	
1468	rac	
1469	+	
1470	–	
1471	rac	
1472	+	
1473	–	
1474	rac	
1475	+	
1476	–	
1477	rac	
1478	+	
1479	–	
1480	rac	
1481	+	

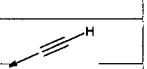
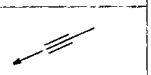
1482	–	
1483	rac	
1484	+	
1485	–	
1486	rac	
1487	+	
1488	–	
1489	rac	
1490	+	
1491	–	
1492	rac	
1493	+	
1494	–	
1495	rac	
1496	+	
1497	–	
1498	rac	
1499	+	
1500	–	

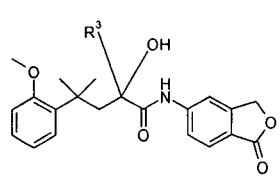
N.°	Racémico o enantiómero	R3
1501	rac	
1502	+	
1503	–	
1504	rac	
1505	+	
1506	–	
1507	rac	
1508	+	

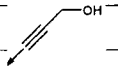
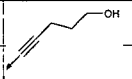
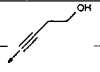
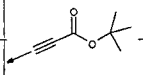
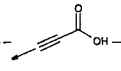
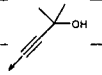
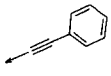
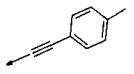


1509	-	
1510	rac	
1511	+	
1512	-	
1513	rac	
1514	+	
1515	-	
1516	rac	
1517	+	
1518	-	
1519	rac	
1520	+	
1521	-	
1522	rac	
1523	+	
1524	-	
1525	rac	
1526	+	
1527	-	
1528	rac	
1529	+	
1530	-	
1531	rac	
1532	+	
1533	-	
1534	rac	
1535	+	
1536	-	
1537	rac	
1538	+	

1539	–	
1540	rac	
1541	+	
1542	–	
1543	rac	
1544	+	
1545	–	
1546	rac	
1547	+	
1548	–	
1549	rac	
1550	+	
1551	–	
1552	rac	
1553	+	
1554	–	
1555	rac	
1556	+	
1557	–	
1558	rac	
1559	+	
1560	–	

N.°	Racémico o enantiómero	R3
1561	rac	
1562	+	
1563	–	
1564	rac	
1565	+	



1566	-	
1567	rac	
1568	+	
1569	-	
1570	rac	
1571	+	
1572	-	
1573	rac	
1574	+	
1575	-	
1576	rac	
1577	+	
1578	-	
1579	rac	
1580	+	
1581	-	
1582	rac	
1583	+	
1584	-	
1585	rac	
1586	+	
1587	-	
1588	rac	
1589	+	
1590	-	
1591	rac	
1592	+	
1593	-	
1594	rac	
1595	+	

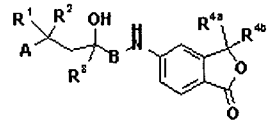
mento para la terapia y la prevención de carcinomas de próstata.

24. Uso de compuestos de acuerdo con una de las reivindicaciones 1 a 13 para la preparación de un medicamento para la terapia de reemplazo hormonal femenina.

25. Uso de compuestos de acuerdo con una de las reivindicaciones 1 a 13 para el control de la fertilidad femenina.

RESUMEN

La presente invención se refiere a moduladores no esteroides del receptor de progesterona de la fórmula general I,



(I)

al proceso para su producción, al uso de los moduladores del receptor de progesterona para la preparación de agentes farmacéuticos así como también composiciones farmacéuticas que contienen estos compuestos. Los compuestos según la invención son apropiados para la terapia y la prevención de enfermedades ginecológicas tales como endometriosis, leiomiomas de útero, hemorragias disfuncionales y dismenorrea y para la terapia y la prevención de tumores dependientes de hormonas y para el uso para el control de la fertilidad femenina y para la terapia de reemplazo hormonal.

PATENT COOPERATION TREATY PCT/EP2006/006532

425

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

BAYER SCHERING PHARMA AKTIENGESELLSCHAFT
Patents & Licensing
13342 Berlin
ALLEMAGNE

Date of mailing *(day/month/year)* 28 August 2007 (28.08.2007)	
Applicant's or agent's file reference 53338AWO	IMPORTANT NOTIFICATION
International application No. PCT/EP2006/006532	International filing date *(day/month/year)* 22 June 2006 (22.06.2006)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address	State of Nationality	State of Residence
SCHERING AKTIENGESELLSCHAFT Müllerstrasse 178 13353 Berlin Germany		DE
	Telephone No. 030 46818718	
	Facsimile No. 030 46812058	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☒ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address	State of Nationality	State of Residence
BAYER SCHERING PHARMA AKTIENGESELLSCHAFT Müllerstrasse 178 13353 Berlin Germany		DE
	Telephone No. 030 46818718	
	Facsimile No. 030 46812058	
	Teleprinter No.	

3. Further observations, if necessary:
The above change has also been recorded in respect of the address for correspondence, as indicated in the addressee box at the top of this form.

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☒ the International Preliminary Examining Authority
☐ the designated Offices concerned
☒ the elected Offices concerned
☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Nissen Diana
Facsimile No. +41 22 338 82 70	e-mail Diana.Nissen@wipo.int Telephone No. +41 22 338 80 54

Form PCT/IB/306 (October 2005) 1/DDAB57380

426

Declaración bajo art. 19 (1) PCT

El solicitante reemplaza las reivindicaciones de la siguiente manera según art. 19 de PCT:

reivindicación 1 como así también reivindicaciones 12 - 16 no han sido modificadas,

reivindicaciones 2 - 11 han sido modificadas de acuerdo con la opinión escrita de la autoridad internacional de búsqueda, formulario PCT/ISA/237, hoja 3, a fin de eliminar la palabra "preferentemente",

reivindicación 17 ha sido reformulada a fin de aclarar que la reivindicación está dirigida a un primer uso medico,

reivindicación 18 - 25 han sido modificadas a fin de especificar la relación con las reivindicaciones 1 - 13 y

la reivindicación 26 ha sido eliminada.

Aseguramos a nuestro mejor entender que no ha sido agregada materia nueva inadmisible a la solicitud por las enmiendas realizadas.

firma ilegible
Dr. Ina Scherlitz-Hofmann
Schering Aktiengesellschaft
Corporate Patents

firma ilegible
Astrid Hinze

Statement under Article 19(1) PCT

Under Article 19 of the PCT hereby applicant submits the replacement of claims as follows:

Claims 1 as well as claims 12 – 16 have not been changed,

claims 2 – 11 have been changed according to the Written Opinion of the International Searching Authority, Form PCT/ISA/237, sheet 3, in order to delete the wording "preferably",

claim 17 has been rephrased so as to clarify that the claim is directed to the first medical use,

claims 18 – 25 have been amended in order to specify the relation to claims 1 – 13 and

claim 26 has been deleted.

We warrant that, to the best of our knowledge, no inadmissible new subject matter has been introduced into the application by the amendments performed.

Dr. Ina Scherlitz-Hofmann

Astrid Hinze

SCHERING AKTIENGESELLSCHAFT

Corporate Patents

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D307/83 C07D307/94 C07D407/12 A61K31/335 A61P15/00
A61P35/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/075915 A (SCHERING AG; SCHMEES, NORBERT; LEHMANN, MANFRED; FUHRMANN, ULRIKE; MUH) 18 September 2003 (2003-09-18) the whole document	1-26
A	US 2002/094983 A1 (ZHANG PUWEN ET AL) 18 July 2002 (2002-07-18) the whole document	1-26
A	WO 00/66590 A (LIGAND PHARMACEUTICALS, INC; AMERICAN HOME PRODUCTS CORPORATION; ZHI,) 9 November 2000 (2000-11-09) the whole document	1-26

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 August 2006	11/08/2006

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	Fritz, M

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03075915 A	18-09-2003	AU 2003209720 A1	22-09-2003
		BR 0308394 A	25-01-2005
		CA 2478948 A1	18-09-2003
		CN 1652768 A	10-08-2005
		HR 20040923 A2	31-12-2004
		JP 2005526064 T	02-09-2005
		MX PA04008881 A	07-12-2004
US 2002094983 A1	18-07-2002	US 6358948 B1	19-03-2002
WO 0066590 A	09-11-2000	AU 4501800 A	17-11-2000
		CA 2371273 A1	09-11-2000
		CN 1353717 A	12-06-2002
		EP 1175422 A2	30-01-2002

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 07-135475- -00000-0000

Fecha: 2007-12-21 17:25:19 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 379 FASENACIONALII
Act: 411 PRESENTACION Folios: 430

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 [ ]

Claudia M Nieva Cortes
Firma Responsable

Fecha_____

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