Organizacion CSA Ltda

Organizacion CSA Ltda

Industria y Comercio

SUPERINTENDENCIA

PCT

"SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO"
INVENTARIO

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISIÓN DE NUEVAS CREACIONES

07-135474

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: MODULARES NO ESTEROIDES DE RECEPTOR DE PROGESTERONA

CLASIFICACIÓN INTERNACIONAL: A61K31/536 // A61P5/34

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. 07-135474- -00000-0000
Fecha: 2007-12-21 17:23:27 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 379 FASENACIONALII
Act: 411 PRESENTACION Folios: 458

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL **P2007/000221**

(1) **SOLICITUD DE:**

[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/EP2006/006531 Fecha Junio 22, 2006
Publicación Internacional No. WO/2006/136461 Fecha Diciembre 28, 2006

(6) **Título (54):** MODULARES NO ESTEROIDES DE RECEPTOR DE PROGESTERONA

(7) **Clasificación Internacional (51)** C07D 413/12, C07D 265/02, A61K 31/536, A61P 5/34.

(8) **Prioridad**
SI [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
DE	Junio 24, 2005	10 2005 030 292.0

(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. 07-023.402
- [ ] 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

ALEXANDER HILLISCH,
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Nacionalidad: Austriaca

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Alemania
Nacionalidad: Alemana

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

RECIBO DE CAJA APLICADO AL EXPEDIENTE NO. _____

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 103,653
FECHA : DICIEMBRE 20 DE 2007

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 07-135474- -00000-0000
Fecha: 2007-12-21 17:23:27 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 379 FASENACIONALII
Act: 411 PRESENTACION Folios: 458

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
OLA 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 : _____

N 007422051

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 10°, 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-

CECBA - LEY404 GCBA LEGALIZACION 07031211734 6 12/03/2007 13:51:46 $20.00

CECBA - LEY404 GCBA APOSTILLE 07031205471 3 12/03/2007 13:51:54 $39.00

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-

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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 modelos 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 en 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

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a juicios verbales, declinar y prorrogar de jurisdicción, tachar, recusar, apelar, transar, 26
someter a arbitraje o mediación, hacer renuncias, exigir y dar cauciones, pedir embar- 27
gos preventivos, definitivos o inhibiciones y su levantamiento, pedir la venta de los 28
bienes de los deudores, solicitar y obtener el cumplimiento de sentencias, prestar ju- 29
ramentos, decir de nulidad, desistir, percibir, otorgar recibos y en general practicar 30
todos los actos y diligencias que sean precisos al desempeño de este mandato. Podrán 31
asimismo substituir el presente poder en todo o en parte.- Dado y firmado en Berlín 32
(Sigue fecha en idioma inglés). Bayer Schering Pharma AG (Sigue texto en idioma 33
inglés). ppa. Sigue una firma ilegible. (Aclarado:) Dr. Noeske-Jungblut. ppa. Sigue 34
otra firma ilegible. (Aclarado:) Dr. Klose". ES COPIA FIEL, doy fe.- En hoja adjunta 35
consta la certificación notarial de las firmas obrantes en el poder en idioma alemán, 36
efectuada el 22 de enero de 2007 por el Escribano Dimitri Rempen, de Berlín, Alema- 37
nia, y a continuación consta la respectiva legalización de la firma y sello del nombra- 38
do Notario (Sello de Apostilla de la Convención de La Haya del 5 de octubre de 39
1961), en idioma alemán, efectuada por el Presidente del Tribunal Regional de Berlín, 40
Alemania.- En hojas adjuntas sigue la referida traducción al idioma nacional la que 41
transcripta textualmente, dice: "TRADUCCIÓN PUBLICA – (Sobre papel con mem- 42
brete de "MOELLER y CO" - América Latina - Agentes de la Propiedad Intelectual - 43
figura un Poder otorgado por la Sociedad "BAYER SCHERING PHARMA AG", con 44
sede en Berlín, Alemania, redactado en idioma nacional, luego del que aparecen los 45
siguientes textos, que traducidos dicen:) "BAYER SCHERING PHARMA AG" – 46
Patentes y licencias – (Firmado y Aclarado:) pp Dr. Noeske-Jungblut – pp (Firmado y 47
Aclarado:) Dr. Klose.- La versión en inglés es para su información únicamente.- Re- 48
gistro de Actas N° R 17/2007.- Me he referido a la prohibición de intervención según 49
el artículo 3, párrafo 1, N° 7, de la Ley de Certificaciones. Mi pregunta de si ha existi- 50

N 007422053

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 tiempo 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, N° 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 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 N° 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 reciente, 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

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LEGALIZACION

10

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 Nº 070312117346/0 La presente legalización no juzga sobre contenido y forma del documento.

Buenos Aires, Lunes 12 de Marzo de 2007

ESC. EDDA ENRIQUETA SINELLI
COLEGIO DE ESCRIBANOS
CONSEJERA

CONSEJERO

APOSTILLE

REPUBLICA ARGENTINA

(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

10. Firma

SUBDIRECTOR ALVARO
COLEGIO DE ESCRIBANOS
CONSEJERO

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

(19) World Intellectual Property Organization
International Bureau

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28 December 2006 (28.12.2006)

PCT

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C07D 265/02 (2006.01) *A61P 5/34* (2006.01)

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PCT/EP2006/006531

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(26) Publication Language: English

(30) Priority Data:
10 2005 030 292.0 24 June 2005 (24.06.2005) DE

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

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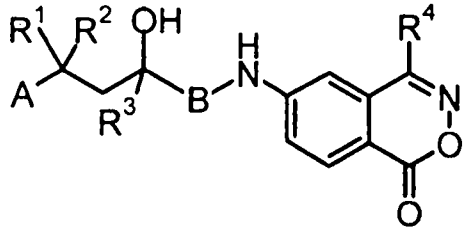
(54) Title: NON-STEROIDAL PROGESTERONE RECEPTOR MODULATORS



(I)

(57) **Abstract:** The present invention relates to non-steroidal progesterone receptor modulators of the general formula (I), a process for their preparation, the use of the progesterone receptor modulators for producing medicaments, and pharmaceutical compositions comprising these compounds. The compounds according to the invention are suitable for the therapy and prophylaxis of gynaecological disorders such as endometriosis, leiomyomas of the uterus, dysfunctional (bleeding)and dysmenorrhoea, and for the therapy and prophylaxis of hormone-dependent tumours and for use for female fertility control and for hormone replacement therapy.

WO 2006/136461 A2

Non-steroidal progesterone receptor modulators

The present invention relates to non-steroidal progesterone receptor modulators, to a process for their preparation, to the use of the progesterone receptor modulators for producing medicaments, and to pharmaceutical compositions which comprise these compounds.

The steroid hormone progesterone controls in a decisive manner the reproductive process in the female body. Progesterone is secreted in large quantities during the cycle and pregnancy respectively by the ovary and the placenta. Progesterone in cooperation with oestrogens brings about cyclic changes in the uterine mucosa (endometrium) during the menstrual cycle. Elevated progesterone levels after ovulation influence the uterine mucosa to convert it into a state permitting nidation of an embryo (blastocyst). During pregnancy, progesterone controls the relaxation of the myometrium and maintains the function of the decidual tissue.

It is further known that progesterone inhibits endometrial proliferation by suppressing oestrogen-mediated mitosis in uterine tissue (K. Chwalisz, R.M. Brenner, U. Fuhrmann, H. Hess-Stumpp, W. Elger, Steroids 65, 2000, 741-751).

Progesterone and progesterone receptors are also known to play a significant part in pathophysiological processes. Progesterone receptors have been detected in the foci of endometriosis, but also in tumours of the uterus, of the breast and of the CNS. It is further known that uterine leiomyomas grow progesterone-dependently.

The effects of progesterone in the tissues of the genital organs and in other tissues occur through interactions with progesterone receptors which are responsible for the cellular effects.

Progesterone receptor modulators are either pure agonists or inhibit the effect of progesterone partly or completely. Accordingly, substances are defined as pure agonists, partial agonists (SPRMs) and pure antagonists.

In accordance with ability of progesterone receptor modulators to influence the effect of the progesterone receptor, these compounds have a considerable potential as

therapeutic agents for gynaecological and oncological indications and for obstetrics and fertility control.

Pure progesterone receptor antagonists completely inhibit the effect of progesterone on the progesterone receptor. They have anti-ovulatory properties and the ability to inhibit oestrogen effects in the endometrium, as far as complete atrophy. They are therefore particularly suitable for intervening in the female reproductive process, e.g. post-ovulation, in order to prevent nidation, during pregnancy in order to increase the reactivity of the uterus to prostaglandins or oxytocin, or in order to achieve opening and softening ("ripening") of the cervix, and to induce a great readiness of myometrium to contract.

A beneficial effect on the pathological event is expected in foci of endometriosis and in tumour tissues which are equipped with progesterone receptors after administration of pure progesterone receptor antagonists. There might be particular advantages for influencing pathological states such as endometriosis or uterine leiomyomas if ovulation inhibition can additionally be achieved by the progesterone receptor antagonists. Ovulation inhibition also dispenses with some of the ovarian hormone production and thus the stimulating effect, deriving from this proportion, on the pathologically altered tissue.

The first progesterone receptor antagonist described, RU 486 (also mifepristone), was followed by a large number of analogues with progesterone receptor-antagonistic activity of varying strength. Whereas RU 486 shows an antiglucocorticoid effect in addition to the progesterone receptor-antagonistic effect, compounds synthesized later are notable in particular for a more selective effect as progesterone receptor antagonists.

Besides steroidal compounds such as onapristone or lilopristone, which are notable by comparison with RU 486 for a better dissociation of the progesterone receptor-antagonistic effect and the antiglucocorticoid effect, also known from the literature are various non-steroidal structures whose antagonistic effect on the progesterone receptor is being investigated [see, for example, 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)]. However, compounds disclosed to date have only moderate antagonistic activity compared with the known steroidal structures. The most effective non-steroidal compounds are

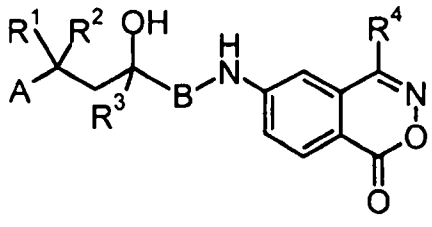
reported to have *in vitro* activities which are 10% of the activity of RU 486.

The antiglucocorticoid activity is disadvantageous for therapeutic use, where the inhibition of progesterone receptors is at the forefront of the therapy. An antiglucocorticoid activity causes unwanted side effects at the dosages necessary for therapy. This may prevent administration of a therapeutically worthwhile dose or lead to discontinuation of the treatment.
Partial or complete reduction of the antiglucocorticoid properties is therefore an important precondition for therapy with progesterone receptor antagonists, especially for those indications requiring treatment lasting weeks or months.

In contrast to the pure antagonists, partial progesterone receptor agonists (SPRMs) show a residual agonistic property which may vary in strength. This leads to these substances showing potentially agonistic effects on the progesterone receptor in certain 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 effect may be of therapeutic benefit for the described indications.

It is therefore an object of the present invention to provide further non-steroidal progesterone receptor modulators. These compounds are intended to have a reduced antiglucocorticoid effect and therefore be suitable for the therapy and prophylaxis of gynaecological disorders such as endometriosis, leiomyomas of the uterus, dysfunctional bleeding and dysmenorrhoea. The compounds according to the invention are additionally intended to be suitable for the therapy and prophylaxis of hormone-dependent tumours, for example of breast, endometrial, ovarian and prostate carcinomas. The compounds are intended furthermore to be suitable for use in female fertility control and for female hormone replacement therapy.

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



(I),

in which

R^1 and R^2 are independently of one another a hydrogen atom, a linear or nonlinear, branched or unbranched C_1-C_5-alkyl group, further forming together with the C atom of the chain a ring having a total of 3-7 members,

R^3 is a radical C≡C-R^a, where

R^a is a hydrogen or a C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_3-C_{10}-cycloalkyl, heterocycloalkyl optionally substituted one or more times, identically or differently, by K, or an aryl or heteroaryl optionally substituted one or more times, identically or differently by 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, -C=NOR^b -NR^cR^d or C_3-C_{10}-cycloalkyl, heterocycloalkyl optionally substituted one or more times, identically or differently, by M, or aryl or heteroaryl optionally substituted one or more times by L,

L is C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, 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 $-(CH_2)_{n+2}-$, where n is 1 or 2, and the terminal oxygen atoms and/or carbon atoms are linked to directly adjacent ring carbon atoms,

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

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

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

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

R^e is a hydrogen, C_1-C_6-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, 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 $C=C-R^gR^h$, where

R^g and R^h are independently of one another a hydrogen or a C_1-C_8-alkyl, C_2-C_8-alkenyl or C_2-C_8-alkynyl optionally substituted one or more times, identically or differently, by 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

mentioned before for R^b, R^c and R^d, and

R^4 is a hydrogen atom, a methyl or an ethyl group or a partly or completely fluorinated C_1-C_3-alkyl group,

A is a mono- or bicyclic carbocyclic or heterocyclic aromatic ring which may optionally be substituted one or more times by C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_6-perfluoroalkyl, C_1-C_6-perfluoroalkoxy, C_1-C_6-alkoxy-C_1-C_8-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 $-(CH_2)_{n+2}$-, where n is 1 or 2, and the terminal oxygen atoms and/or carbon atoms are linked to directly adjacent ring carbon atoms, or

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

or

A is an alkenyl group $-CR^5$=CR^6R^7, where

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

A is an alkynyl group $-C\equiv CR^5$, with the meaning stated above for R^5, and

B is a carbonyl or a CH_2 group,

and their pharmaceutically acceptable salts.

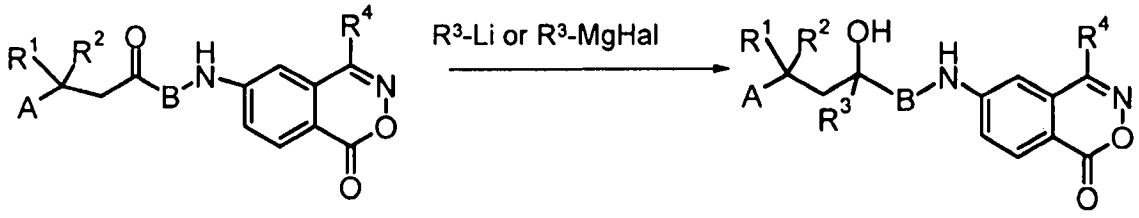
The compounds according to the invention of the general formula I may, owing to the presence of centres of asymmetry, exist as different stereoisomers. Both the racemates and the separate stereoisomers belong to the subject matter of the present invention.

The present invention further includes the novel compounds as active pharmaceutical ingredients, the preparation thereof, their therapeutic use and pharmaceutical dosage forms which comprise the novel substances.

The compounds according to the invention of the general formula (I) or their pharmaceutically acceptable salts can be used to produce a medicament, in particular for the treatment and prophylaxis of gynaecological disorders such as endometriosis, leiomyomas of the uterus, dysfunctional bleeding and dysmenorrhoea. The compounds according to the invention may further be used for the treatment and prophylaxis of hormone-dependent tumours such as, for example, for breast, prostate and endometrial carcinoma.

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

The present invention additionally relates to a process for preparing the compounds of the general formula (I). The substituent R^3 is introduced by selective addition reaction of organometallic compounds such as lithium alkynyls or magnesium haloalkynyls onto a keto group. This leads either directly or after carrying out further modificiations to the compounds according to the invention of the general formula (I).



The compounds according to the invention are prepared by selective addition of organometallic compounds onto keto amides which have been described for example in the published specifications US 2002/0077356, US 6,323,199B1, WO 200375915 and WO 9854159. The organometallic compounds may be for example lithium alkynyl or magnesium haloalkynyl compounds. These are generated for example by reacting the appropriate alkynes with butyllithium or Grignard compounds. The corresponding

organometallic alkenyl compounds can also be prepared in analogy thereto. The reactivity of the keto groups is in this case distinctly higher by comparison with the amide carbonyl and with the benzoxazinone, so that a selective addition is achieved on suitable choice of the reaction conditions. Alternatively, the alkynyl or alkenyl radicals introduced as R^3 can also be further modified later. Reactions suitable for these modifications are those known to the skilled person, such as oxidation, reduction, substitution, alkylation, palladium-catalysed reaction. Any protective groups present are eliminated at a suitable time.

The non-steroidal compounds according to the invention of the general formula I have strong antagonistic or strong partial agonistic effects on the progesterone receptor. They show a strong dissociation of effects in relation to their strength of binding to the progesterone receptor and to the glucocorticoid receptor. Whereas known progesterone receptor antagonists such as mifepristone (RU 486) show, besides the desired high binding affinity for the progesterone receptor, likewise a high affinity for the glucocorticoid receptor, the compounds according to the invention are notable for a very low glucocorticoid receptor binding with simultaneously a high progesterone receptor affinity.

The substituents, defined as groups, of the compounds according to the invention of the general formula I may in each case have the following meanings:

C_1-C_5-, C_1-C_6- and C_1-C_8-alkyl group means linear or nonlinear, branched or unbranched alkyl radicals. Examples thereof are a methyl, ethyl, n-propyl, isopropyl, n-, iso-, tert-butyl, an n-pentyl, 2,2-dimethylpropyl, 3-methylbutyl, hexyl, heptyl or octyl group.
Preferred in the meaning of R^a in this connection are the methyl, ethyl, n-propyl or n-butyl group and an n-pentyl group.
Preferred in the meaning of R^1 and R^2 are methyl or ethyl.

Alkenyl means linear or nonlinear, branched or unbranched alkenyl radicals. Examples of the meaning of a C_2-C_8-alkenyl group in the context of the invention are the following: vinyl, allyl, 3-buten-1-yl or 2,3-dimethyl-2-propenyl. If the aromatic system A is substituted by a C_2-C_8-alkenyl radical, it is preferably a vinyl group.

Alkynyl means linear or nonlinear, branched or unbranched alkynyl radicals. A C_2-C_8-

alkynyl radical is intended to be for example an ethynyl, propynyl, butynyl, pentynyl, hexynyl and octynyl group, preferably an ethynyl or propynyl group.

Examples which may be mentioned of C_3-C_{10}-cycloalkyl are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Cyclopropyl, cyclopentyl and cyclohexyl are preferred.

Heterocycloalkyl in the meaning of R^a, K and L means 3-8-membered heterocycloalkyl radicals. Examples of heterocycloalkyl are morpholinyl, tetrahydrofuranyl, pyranyl, piperazinyl, piperidinyl, pyrrolidinyl, oxiranyl, oxetanyl, aziridinyl, dioxolanyl and dioxanyl. In this connection, the position of the heteroatom in relation to the point of linkage can be any chemically possible position.

Possible examples of C_1-C_6-alkoxyl-C_1-C_6-alkoxy group are methoxymethoxy, ethoxymethoxy or 2-methoxyethoxy.

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

Suitable for a partly or completely fluorinated C_1-C_5-alkyl group are the perfluorinated alkyl groups above. Of these, preference is given in particular to the trifluoromethyl or pentafluoroethyl group and, partly fluorinated alkyl groups, for example the 5,5,5,4,4-pentafluoropentyl or 5,5,5,4,4,3,3-heptafluoropentyl group.

A halogen atom may be a fluorine, chlorine, bromine or iodine atom. Fluorine, chlorine or bromine is preferred here.

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

The mono- or bicyclic carbocyclic aromatic ring A, which may be substituted more than once, is a carbocyclic or heterocyclic aryl radical.
In the former case it is for example a phenyl or naphthyl radical, preferably a phenyl radical.
It is possible to use as 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, tetrazolyl radical, in particular all the possible isomers in relation to the positions of the heteroatoms.

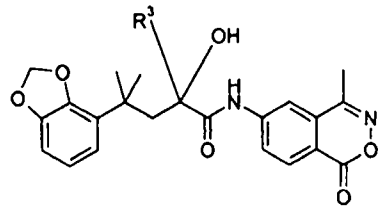
R^3 means in the case of an aryl radical an optionally substituted phenyl, 1- or 2-naphthyl radical, with preference for the phenyl radical. Examples of a heteroaryl radical are the 2-, 3- or 4-pyridinyl, the 2- or 3-furyl, the 2- or 3-thienyl, the 2- or 3-pyrrolyl, the 2-, 4- or 5-imidazolyl, the pyrazinyl, the 2-, 4- or 5-pyrimidinyl or 3- or 4-pyridazinyl radical.

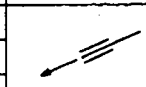
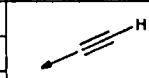
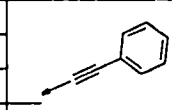
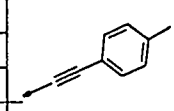
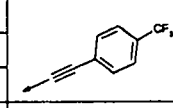
The number p for a $(CH_2)_p$ radical may be a number from 0 to 6, preferably 0 to 2. "Radical" means according to the invention all functional groups stated in connection with $(CH_2)_p$.

In the case where the compounds of the general formula I (B = $-CH_2-$) are in the form of salts, this is possible for example in the form of the hydrochloride, sulphate, nitrate, tartrate, citrate, fumarate, succinate or benzoate.

If the compounds according to the invention are in the form of racemic mixtures, they can be fractionated by methods of racemate resolution familiar to the skilled person into the pure optically active forms. For example, the racemic mixtures can be separated into the pure isomers by chromatography on a support material which is itself optically active (CHIRALPAK AD®). It is also possible to esterify the free hydroxy group in a racemic compound of the general formula I with an optically active acid, and to separate the resulting diastereoisomeric esters by fractional crystallization or chromatography and to hydrolyse the separated esters in each case to the optically pure isomers. It is possible to use as optically active acid for example mandelic acid, camphorsulphonic acid or tartaric acid.

The compounds specified below, and 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	
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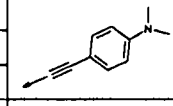
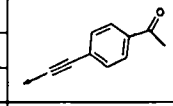
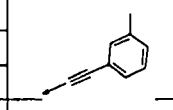
18	-	
19	rac	
20	+	
21	-	
22	rac	
23	+	
24	-	
25	rac	
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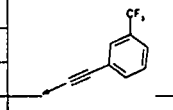
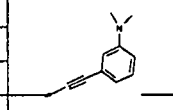
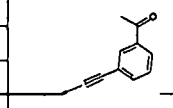
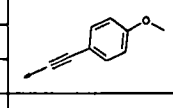
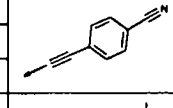
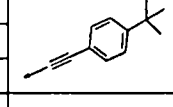
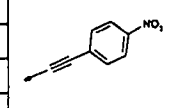
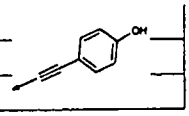
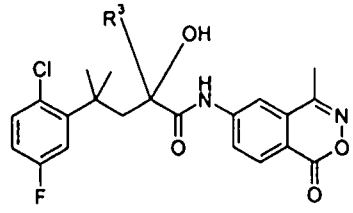
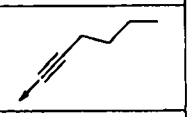
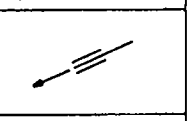
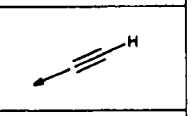
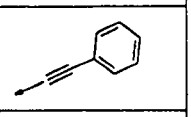
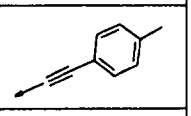
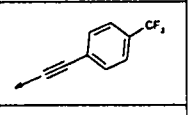
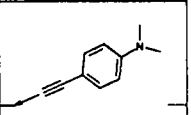
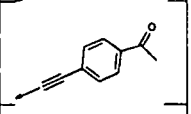
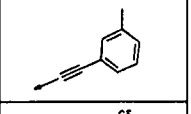
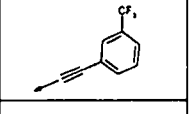
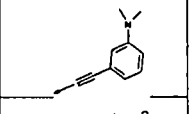
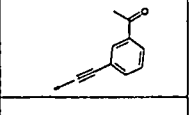
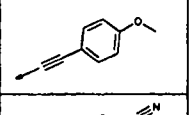
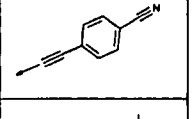
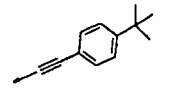
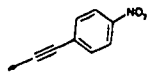
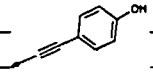
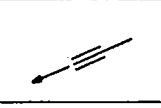
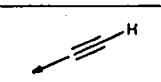
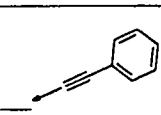
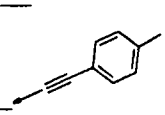
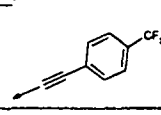
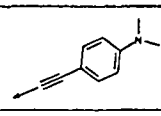
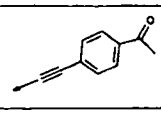
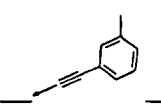
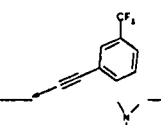
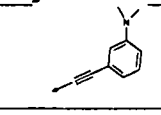
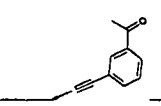
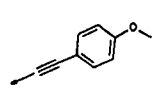
27	-	
28	rac	
29	+	
30	-	
31	rac	
32	+	
33	-	
34	rac	
35	+	
36	-	
37	rac	
38	+	
39	-	
40	rac	
41	+	
42	-	
43	rac	
44	+	
45	-	
46	rac	
47	+	
48	-	

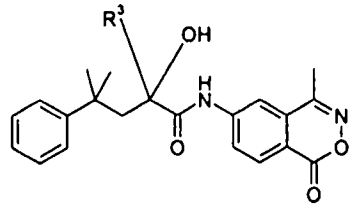
49	rac	
50	+	
51	-	

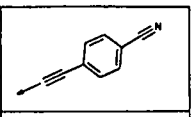
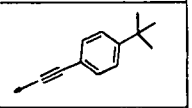
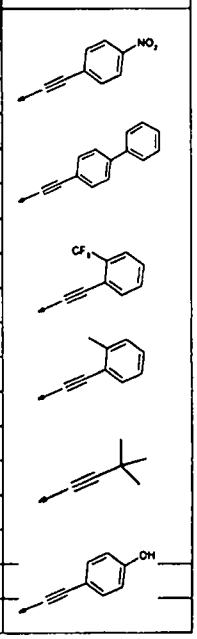


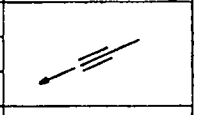
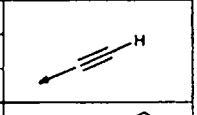
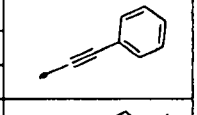
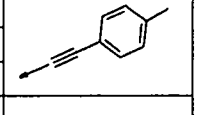
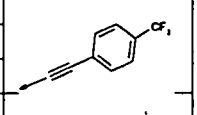
No.	Racemic or enantiomer	R3
52	rac	
53	-	
54	+	
55	rac	
56	+	
57	-	
58	rac	
59	+	
60	-	
61	rac	
62	+	
63	-	
64	rac	
65	+	
66	-	
67	rac	
68	+	
69	-	
70	rac	
71	+	
72	-	
73	rac	
74	+	
75	-	
76	rac	
77	+	
78	-	
79	rac	
80	+	
81	-	
82	rac	
83	+	
84	-	
85	rac	
86	+	
87	-	
88	rac	
89	+	
90	-	
91	rac	
92	+	
93	-	
94	rac	
95	+	
96	-	

97	rac	
98	+	
99	-	
100	rac	
191	+	
102	-	
103	rac	
104	+	
105	-	

No.	Racemic or enantiomer	R3
106	rac	
107	-	
108	+	
109	rac	
110	+	
111	-	
112	rac	
113	+	
114	-	
115	rac	
116	+	
117	-	
118	rac	
119	+	
120	-	
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	-	

No.	Racemic or enantiomer	R3
169	rac	
170	-	
171	+	
172	rac	
173	+	
174	-	
175	rac	
176	+	
177	-	
178	rac	
179	+	
180	-	
181	rac	
182	+	
183	-	
184	rac	
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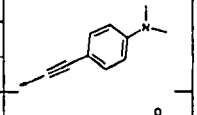
186	-	
187	rac	
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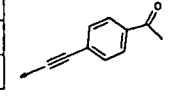
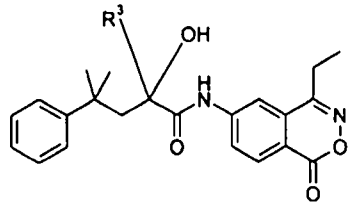
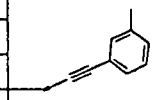
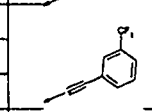
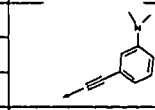
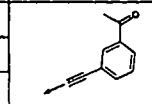
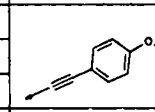
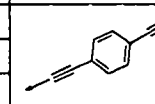
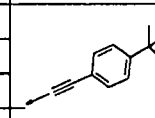
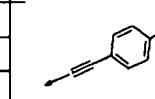
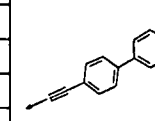
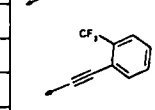
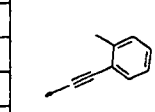
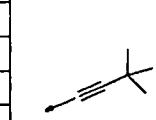
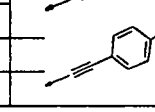
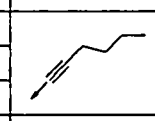
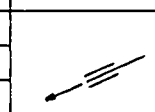
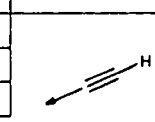
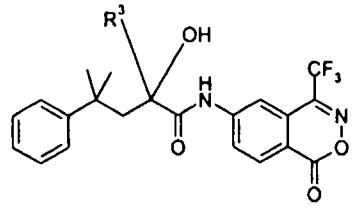
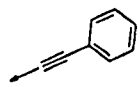
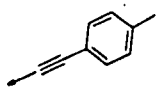
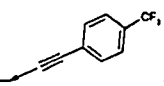
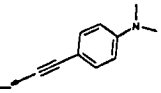
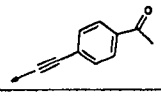
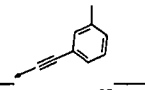
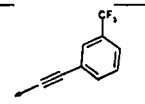
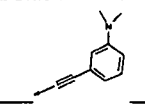
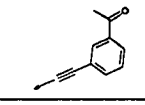
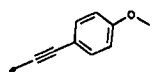
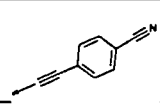
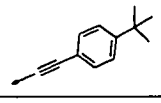
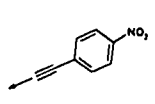
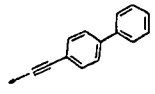
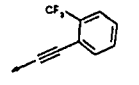
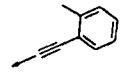
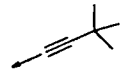
189	-	
190	rac	
191	+	
192	-	

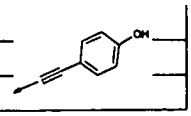


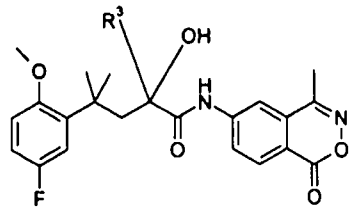
193	rac	
194	+	
195	-	
196	rac	
197	+	
198	-	
199	rac	
200	+	
201	-	
202	rac	
203	+	
204	-	
205	rac	
206	+	
207	-	
208	rac	
209	+	
210	-	
211	rac	
212	+	
213	-	
214	rac	
215	+	
216	-	
217	rac	
218	+	
219	-	
220	rac	
221	+	
222	-	
223	rac	
224	+	
225	-	
226	rac	
227	+	
228	-	
229	rac	
230	+	
231	-	

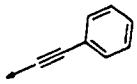
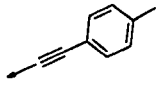
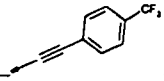
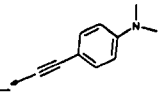
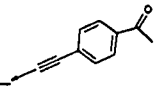
No.	Racemic or enantiomer	R3
232	rac	
233	-	
234	+	
235	rac	
236	+	
237	-	
238	rac	
239	+	
240	-	



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	-	



No.	Racemic or enantiomer	R3
295	rac	
296	-	
297	+	
298	rac	
299	+	
300	-	
301	rac	
302	+	
303	-	
304	rac	
305	+	
306	-	
307	rac	
308	+	
309	-	
310	rac	
311	+	
312	-	
313	rac	
314	+	
315	-	
316	rac	
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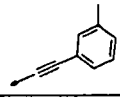
317	-	
319	rac	
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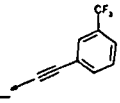
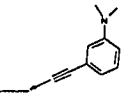
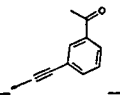
321	-	
322	rac	
323	+	
324	-	
325	rac	
326	+	
327	-	
328	rac	
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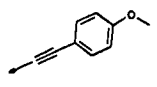
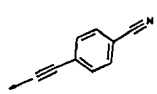
330	-	
331	rac	
332	+	
333	-	
334	rac	
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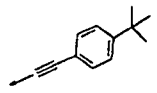
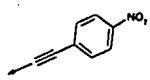
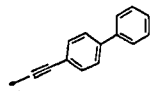
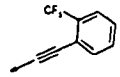
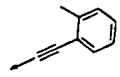
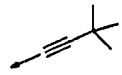
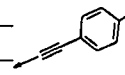
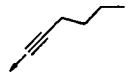
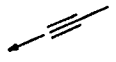
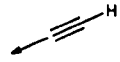
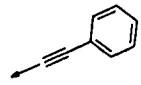
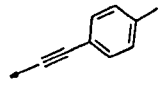
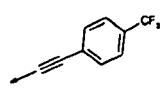
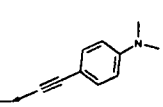
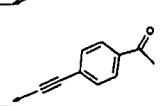
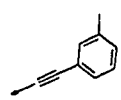
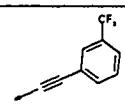
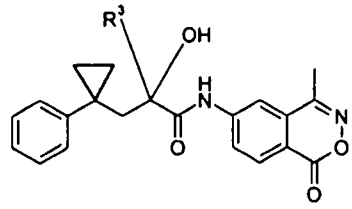
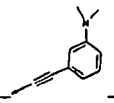
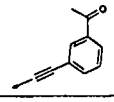
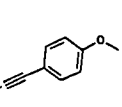
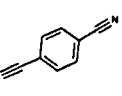
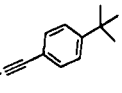
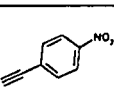
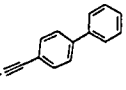
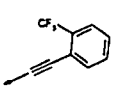
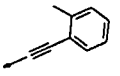
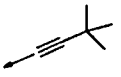
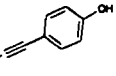
336	-	
337	rac	
338	+	
339	-	

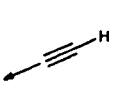
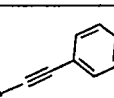
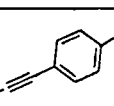
30

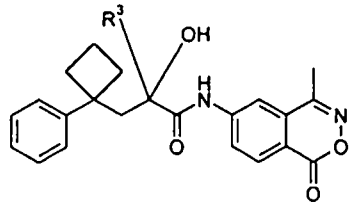
340	rac	
341	+	
342	-	
343	rac	
344	+	
345	-	
346	rac	
347	+	
348	-	
349	rac	
350	+	
351	-	
352	rac	
353	+	
354	-	
355	rac	
356	+	
357	-	

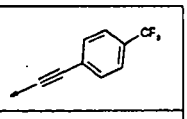
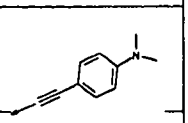
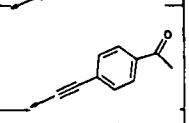
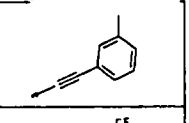
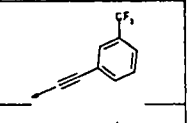
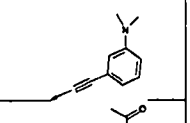
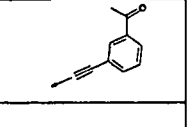
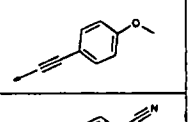
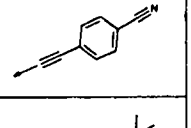
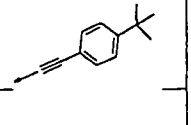
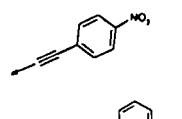
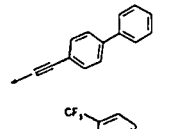
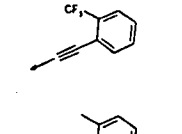
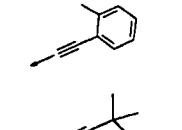
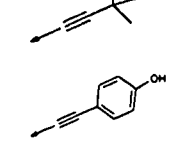
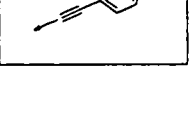
No.	Racemic or enantiomer	R3
358	rac	
359	-	
360	+	
361	rac	
362	+	
363	-	
364	rac	
365	+	
366	-	
367	rac	
368	+	
369	-	
370	rac	
371	+	
372	-	
373	rac	
374	+	
375	-	
376	rac	
377	+	
378	-	
379	rac	
380	+	
381	-	
382	rac	
383	+	
384	-	
385	rac	
386	+	
387	-	

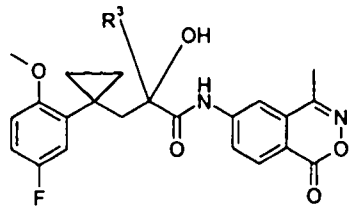


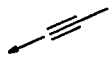
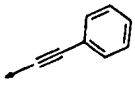
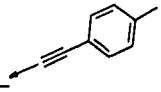
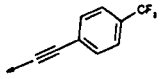
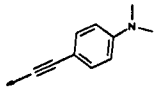
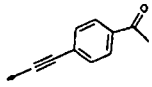
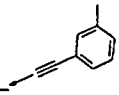
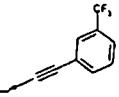
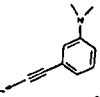
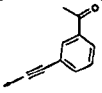
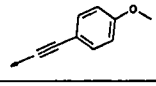
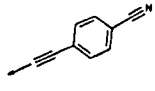
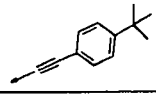
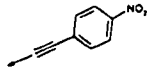
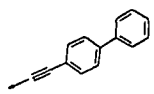
388	rac	
389	+	
390	-	
391	rac	
392	+	
393	-	
394	rac	
395	+	
396	-	
397	rac	
398	+	
399	-	
400	rac	
401	+	
402	-	
403	rac	
404	+	
405	-	
406	rac	
407	+	
408	-	
409	rac	
410	+	
411	-	
412	rac	
413	+	
414	-	
415	rac	
416	+	
417	-	
418	rac	
419	+	
420	-	

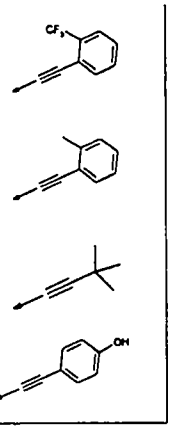
No.	Racemic or enantiomer	R3
421	rac	
422	-	
423	+	
424	rac	
425	+	
426	-	
427	rac	
428	+	
429	-	
430	rac	
431	+	
432	-	
433	rac	
434	+	
435	-	

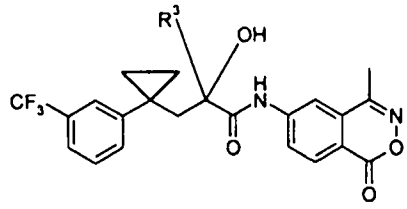


436	rac	
437	+	
438	-	
439	rac	
440	+	
441	-	
442	rac	
443	+	
444	-	
445	rac	
446	+	
447	-	
448	rac	
449	+	
450	-	
451	rac	
452	+	
453	-	
454	rac	
455	+	
456	-	
457	rac	
458	+	
459	-	
460	rac	
461	+	
462	-	
463	rac	
464	+	
465	-	
466	rac	
467	+	
468	-	
469	rac	
470	+	
471	-	
472	rac	
473	+	
474	-	
475	rac	
476	+	
477	-	
478	rac	
479	+	
480	-	
481	rac	
482	+	
483	-	

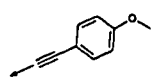
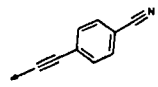
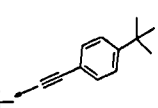
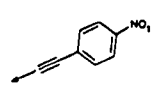
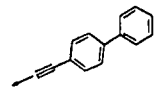
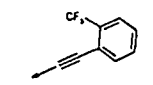
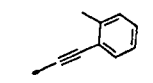
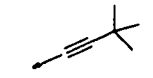
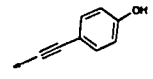


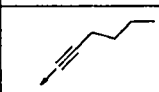
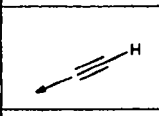
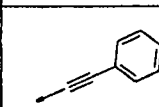
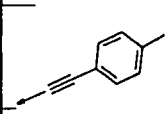
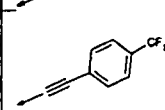
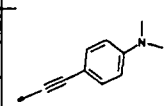
No.	Racemic or enantiomer	R3
484	rac	
485	-	
486	+	
487	rac	
488	+	
489	-	
490	rac	
491	+	
492	-	
493	rac	
494	+	
495	-	
496	rac	
497	+	
498	-	
499	rac	
500	+	
501	-	
502	rac	
503	+	
504	-	
505	rac	
506	+	
507	-	
508	rac	
509	+	
510	-	
511	rac	
512	+	
513	-	
514	rac	
515	+	
516	-	
517	rac	
518	+	
519	-	
520	rac	
521	+	
522	-	
523	rac	
524	+	
525	-	
526	rac	
527	+	
528	-	
529	rac	
530	+	
531	-	
532	rac	
533	+	
534	-	

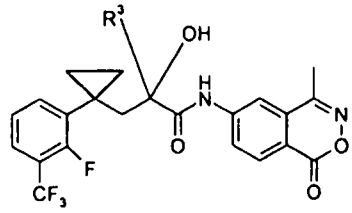
535	rac	
536	+	
537	-	
538	rac	
539	+	
540	-	
541	rac	
542	+	
543	-	
544	rac	
545	+	
546	-	

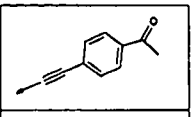
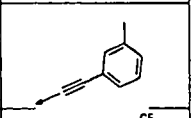
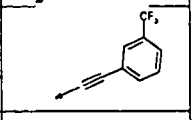
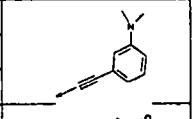
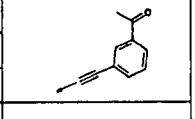


No.	Racemic or enantiomer	R3
547	rac	
548	-	
549	+	
550	rac	
551	+	
552	-	
553	rac	
554	+	
555	-	
556	rac	
557	+	
558	-	
559	rac	
560	+	
561	-	
562	rac	
563	+	
564	-	
565	rac	
566	+	
567	-	
568	rac	
569	+	
570	-	
571	rac	
572	+	
573	-	
574	rac	
575	+	
576	-	
577	rac	
578	+	
579	-	
580	rac	
581	+	
582	-	

583	rac	
584	+	
585	-	
586	rac	
587	+	
588	-	
589	rac	
590	+	
591	-	
592	rac	
593	+	
594	-	
595	rac	
596	+	
597	-	
598	rac	
599	+	
600	-	
601	rac	
602	+	
603	-	
604	rac	
605	+	
606	-	
607	rac	
608	+	
609	-	

No.	Racemic or enantiomer	R3
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	
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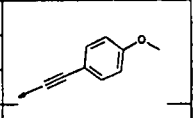
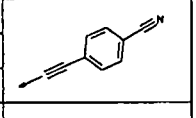
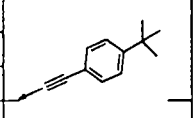
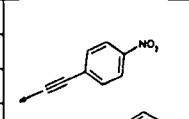
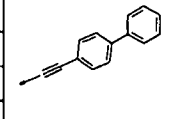
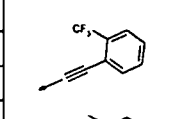
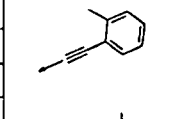
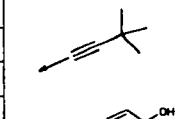
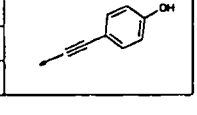
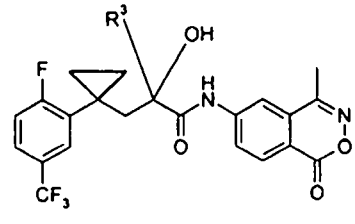
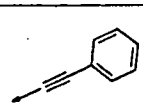
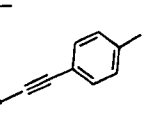
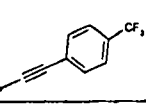
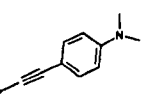
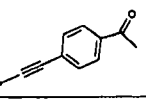
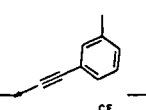
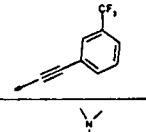
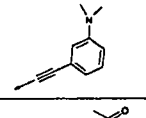
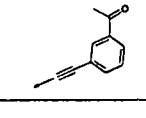
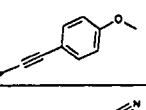
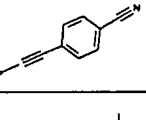
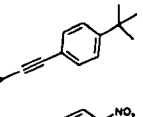
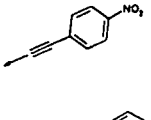
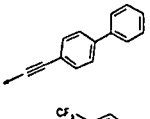
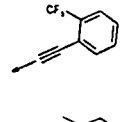
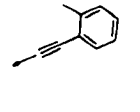
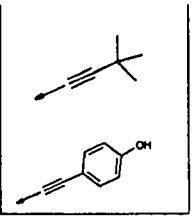
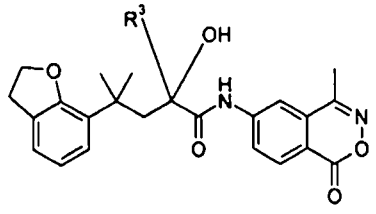
646	rac	
647	+	
648	-	
649	rac	
650	+	
651	-	
652	rac	
653	+	
654	-	
655	rac	
656	+	
657	-	
658	rac	
659	+	
660	-	
661	rac	
662	+	
663	-	
664	rac	
665	+	
666	-	
667	rac	
668	+	
669	-	
670	rac	
671	+	
672	-	

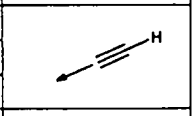
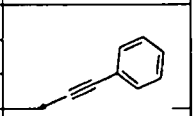
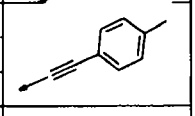
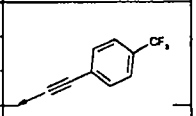
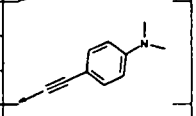
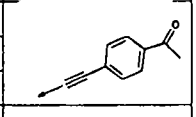
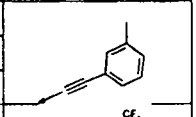
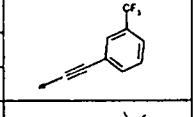
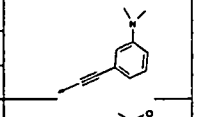
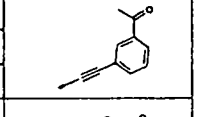
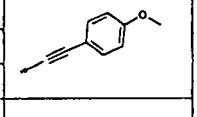
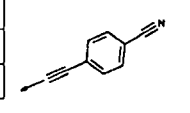
No.	Racemic or enantiomer	R3
673	rac	
674	-	
675	+	
676	rac	
677	+	
678	-	

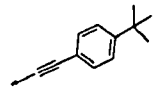
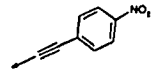
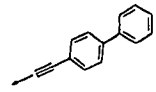
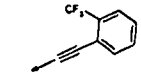


679	rac	
680	+	
681	-	
682	rac	
683	+	
684	-	
685	rac	
686	+	
687	-	
688	rac	
689	+	
690	-	
691	rac	
692	+	
693	-	
694	rac	
695	+	
696	-	
697	rac	
698	+	
699	-	
700	rac	
701	+	
702	-	
703	rac	
704	+	
705	-	
706	rac	
707	+	
708	-	
709	rac	
710	+	
711	-	
712	rac	
713	+	
714	-	
715	rac	
716	+	
717	-	
718	rac	
719	+	
720	-	
721	rac	
722	+	
723	-	
724	rac	
725	+	
726	-	
727	rac	
728	+	
729	-	

730	rac	
731	+	
732	-	
733	rac	
734	+	
735	-	



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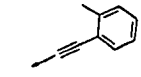
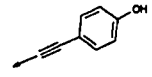
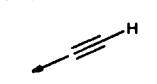
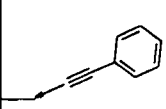
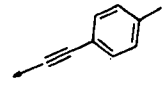
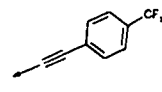
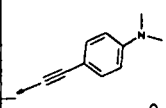
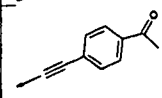
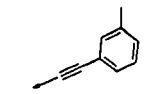
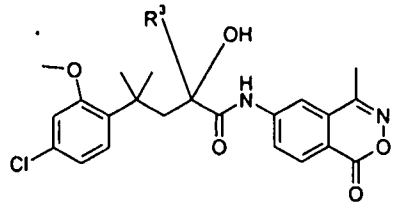
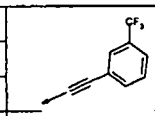
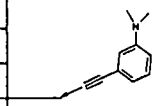
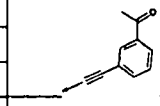
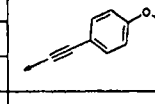
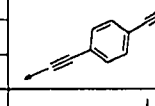
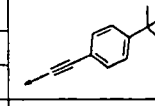
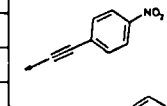
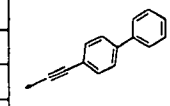
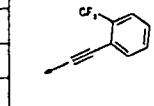
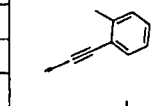
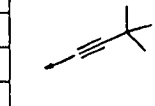
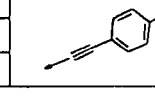
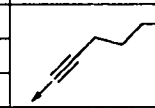
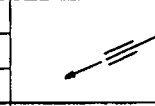
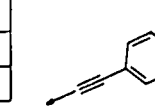
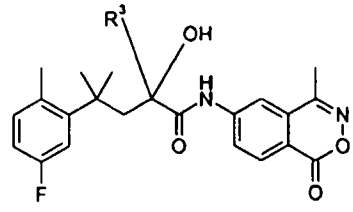
789	-	
790	rac	
791	+	
792	-	
793	rac	
794	+	
795	-	
796	rac	
797	+	
798	-	

No.	Racemic or enantiomer	R3
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	-	

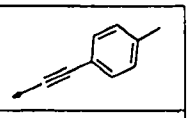
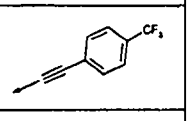
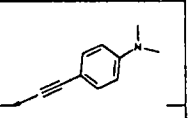
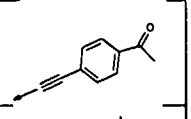
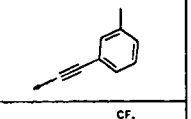
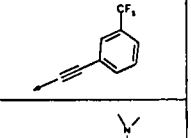
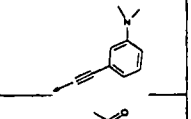
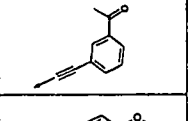
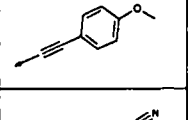
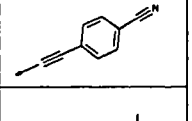
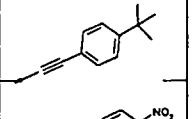
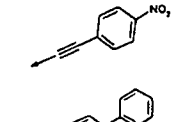
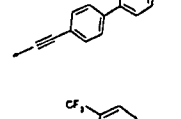
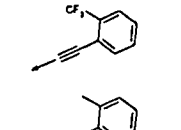
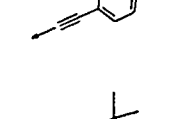
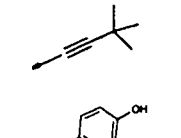
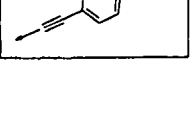


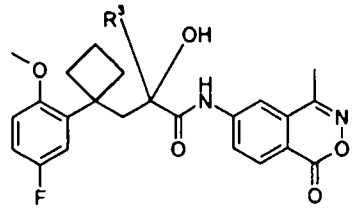
826	rac	
827	+	
828	-	
829	rac	
830	+	
831	-	
832	rac	
833	+	
834	-	
835	rac	
836	+	
837	-	
838	rac	
839	+	
840	-	
841	rac	
842	+	
843	-	
844	rac	
845	+	
846	-	
847	rac	
848	+	
849	-	
850	rac	
851	+	
852	-	
853	rac	
854	+	
855	-	
856	rac	
857	+	
858	-	
859	rac	
860	+	
861	-	

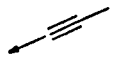
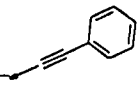
No.	Racemic or enantiomer	R3
862	rac	
863	-	
864	+	
865	rac	
866	+	
867	-	
868	rac	
869	+	
870	-	
871	rac	
872	+	
873	-	



40

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	-	
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	-	



No.	Racemic or enantiomer	R3
925	rac	
926	-	
927	+	
928	rac	
929	+	
930	-	
931	rac	
932	+	
933	-	
934	rac	
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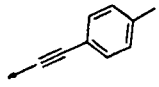
936	-	
937	rac	
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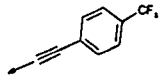
939	-	
940	rac	
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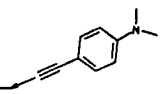
942	-	
943	rac	
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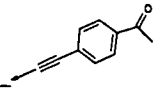
946	rac	
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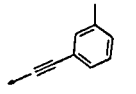
948	-	
949	rac	
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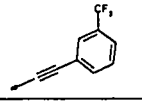
952	rac	
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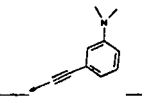
954	-	
955	rac	
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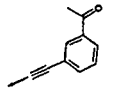
957	-	
958	rac	
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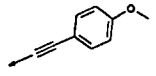
960	-	
961	rac	
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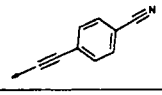
964	rac	
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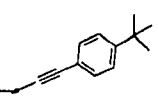
966	-	
967	rac	
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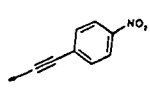
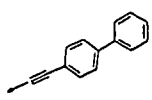
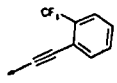
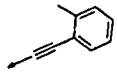
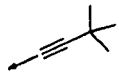
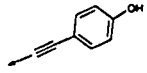
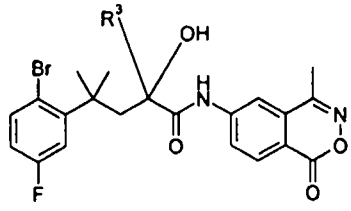
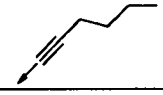
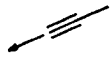
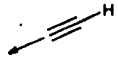
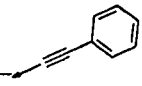
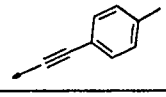
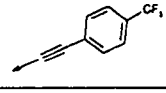
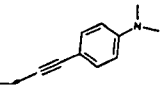
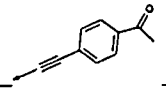
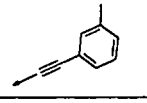
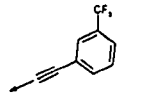
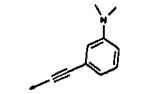
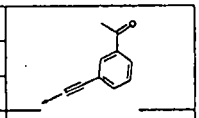
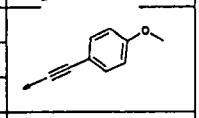
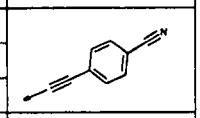
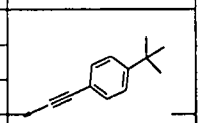
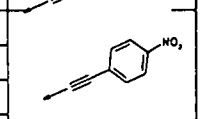
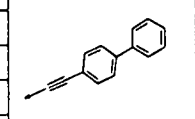
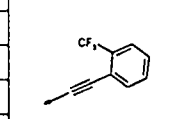
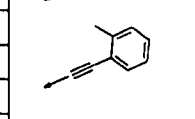
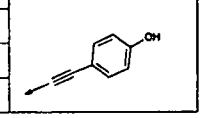
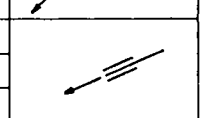
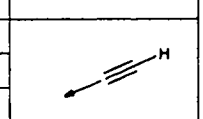
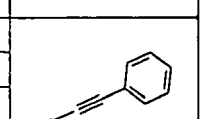
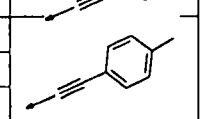
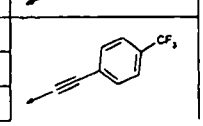
969	-	
970	rac	
971	+	
972	-	

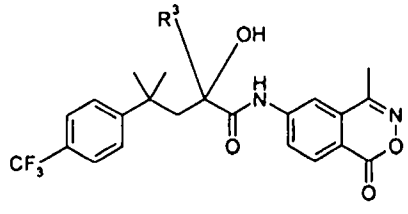
973	rac	
974	+	
975	-	
976	rac	
977	+	
978	-	
979	rac	
980	+	
981	-	
982	rac	
983	+	
984	-	
985	rac	
986	+	
987	-	

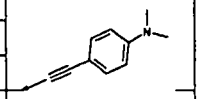
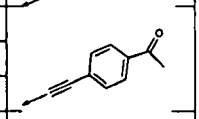


No.	Racemic or enantiomer	R3
988	rac	
989	-	
990	+	
991	rac	
992	+	
993	-	
994	rac	
995	+	
996	-	
997	rac	
998	+	
999	-	
1000	rac	
1001	+	
1002	-	
1003	rac	
1004	+	
1005	-	
1006	rac	
1007	+	
1008	-	
1009	rac	
1010	+	
1011	-	
1012	rac	
1013	+	
1014	-	
1015	rac	
1016	+	
1017	-	
1018	rac	
1019	+	
1020	-	

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	-	

No.	Racemic or enantiomer	R3
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	
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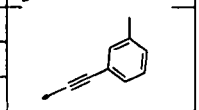
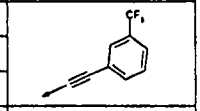
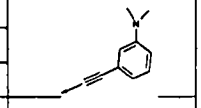
1074	-	
1075	rac	
1076	+	
1077	-	
1078	rac	
1079	+	
1080	-	
1081	rac	
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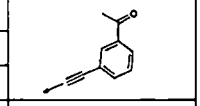
1083	-	
1084	rac	
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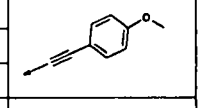
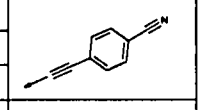
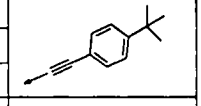
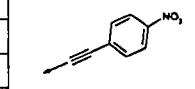
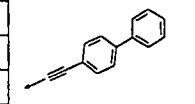
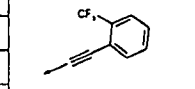
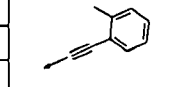
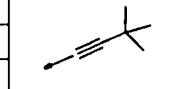
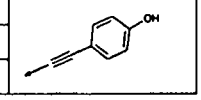
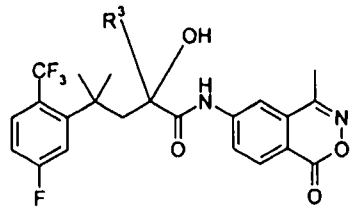
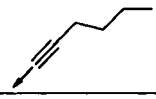
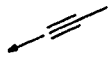
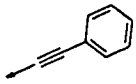
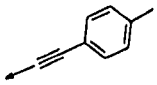
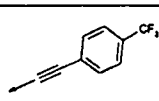
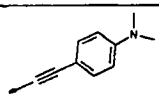
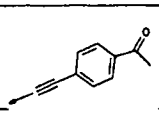
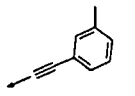
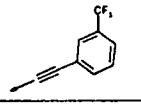
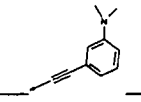
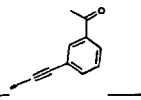
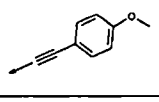
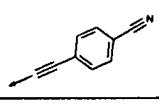
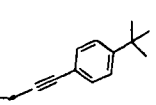
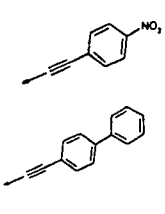
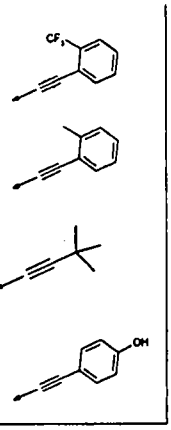
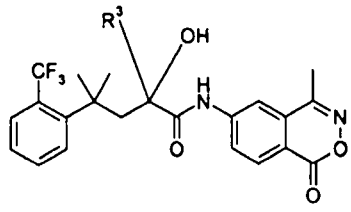
1086	-	
1087	rac	
1088	+	
1089	-	
1090	rac	
1091	+	
1092	-	
1093	rac	
1094	+	
1095	-	
1096	rac	
1097	+	
1098	-	
1099	rac	
1100	+	
1101	-	
1102	rac	
1103	+	
1104	-	
1105	rac	
1106	+	
1107	-	
1108	rac	
1109	+	
1110	-	
1111	rac	
1112	+	
1113	-	

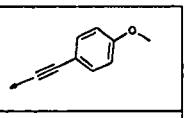
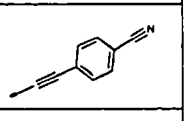
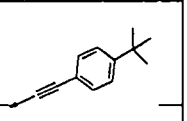
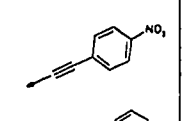
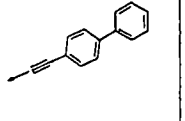
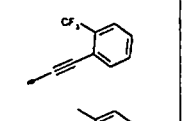
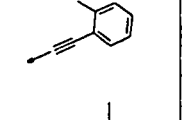
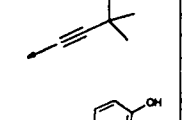
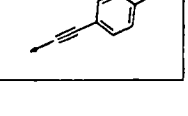


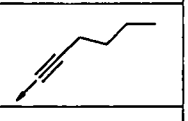
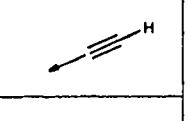
No.	Racemic or enantiomer	R3
1114	rac	
1115	-	
1116	+	
1117	rac	
1118	+	
1119	-	
1120	rac	
1121	+	
1122	-	
1123	rac	
1124	+	
1125	-	
1126	rac	
1127	+	
1128	-	
1129	rac	
1130	+	
1131	-	
1132	rac	
1133	+	
1134	-	
1135	rac	
1136	+	
1137	-	
1138	rac	
1139	+	
1140	-	
1141	rac	
1142	+	
1143	-	
1144	rac	
1145	+	
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	-	

No.	Racemic or enantiomer	R3
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	-	
1202	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	-	

No.	Racemic or enantiomer	R3
1240	rac	
1241	-	
1242	+	
1243	rac	
1244	+	
1245	-	
1246	rac	
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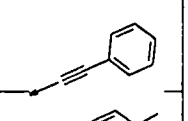
1249	rac	
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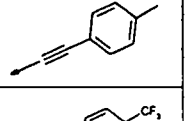
1252	rac	
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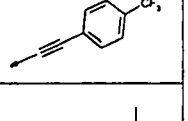
1255	rac	
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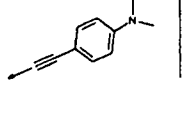
1258	rac	
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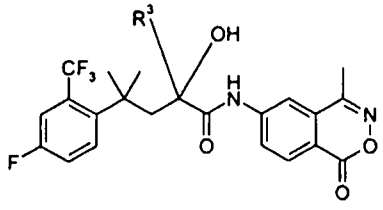
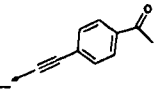
1260	-	



1261	rac	
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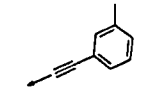
1263	-	
1264	rac	
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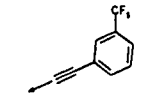
1267	rac	
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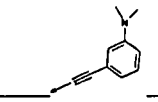
1270	rac	
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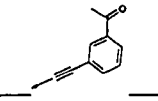
1272	-	
1273	rac	
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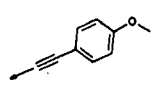
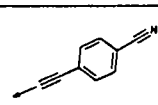
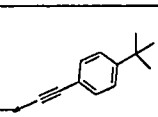
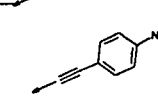
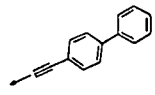
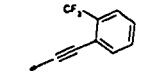
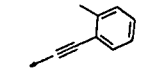
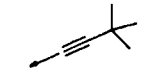
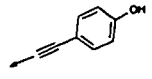
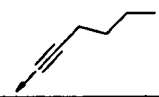
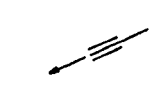
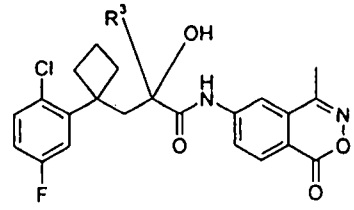
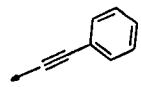
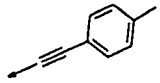
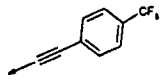
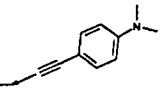
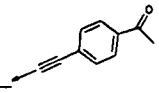
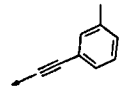
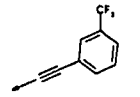
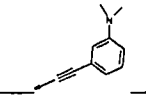
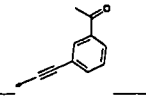
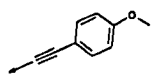
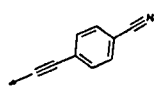
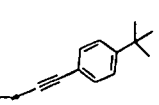
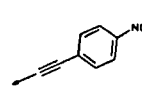
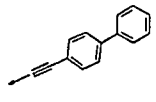
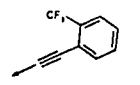
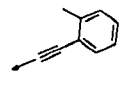
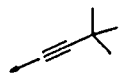
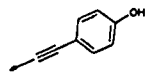
1275	-	
1276	rac	
1277	+	
1278	-	
1279	rac	
1280	+	
1281	-	
1282	rac	
1283	+	
1284	-	
1285	rac	
1286	+	
1287	-	
1288	rac	
1289	+	
1290	-	
1291	rac	
1292	+	
1293	-	
1294	rac	
1295	+	
1296	-	
1297	rac	
1298	+	
1299	-	
1300	rac	
1301	+	
1302	-	

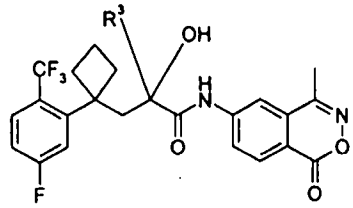
No.	Racemic or enantiomer	R3
1303	rac	
1304	-	
1305	+	
1306	rac	
1307	+	
1308	-	

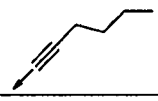
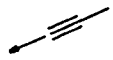
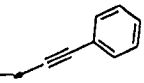
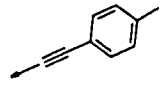
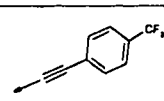
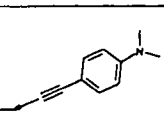
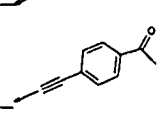
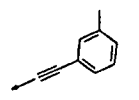
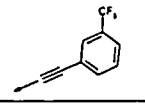
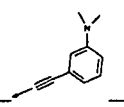
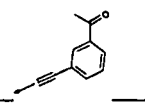
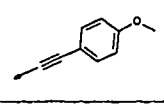
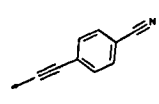


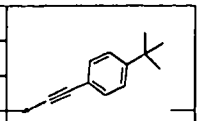
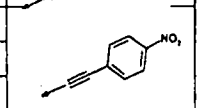
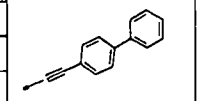
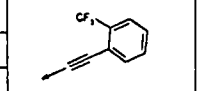
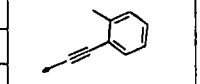
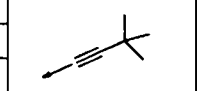
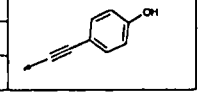
1309	rac	
1310	+	
1311	-	
1312	rac	
1313	+	
1314	-	
1315	rac	
1316	+	
1317	-	
1318	rac	
1319	+	
1320	-	
1321	rac	
1322	+	
1323	-	
1324	rac	
1325	+	
1326	-	
1327	rac	
1328	+	
1329	-	
1330	rac	
1331	+	
1332	-	
1333	rac	
1334	+	
1335	-	
1336	rac	
1337	+	
1338	-	
1339	rac	
1340	+	
1341	-	
1342	rac	
1343	+	
1344	-	
1345	rac	
1346	+	
1347	-	
1348	rac	
1349	+	
1350	-	
1351	rac	
1352	+	
1353	-	
1354	rac	
1355	+	
1356	-	
1357	rac	
1358	+	
1359	-	

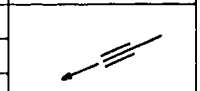
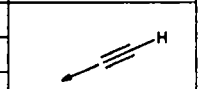
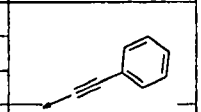
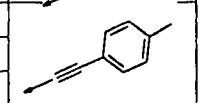
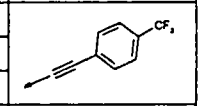
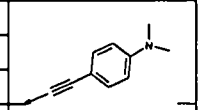
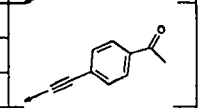
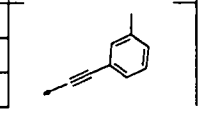
50

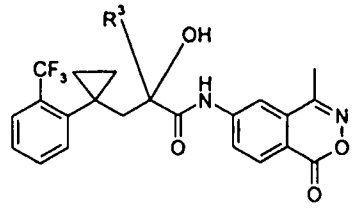
1360	rac	
1361	+	
1362	-	
1362	rac	
1364	+	
1365	-	

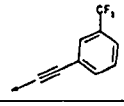
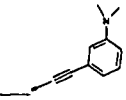
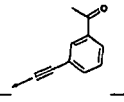
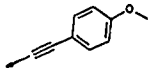
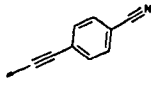
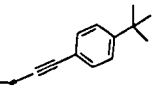
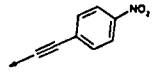
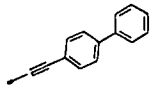
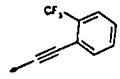
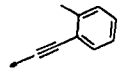
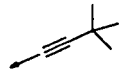
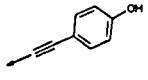


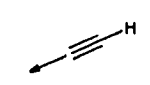
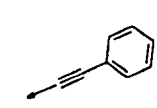
No.	Racemic or enantiomer	R3
1366	rac	
1367	-	
1368	+	
1369	rac	
1370	+	
1371	-	
1372	rac	
1373	+	
1374	-	
1375	rac	
1376	+	
1377	-	
1378	rac	
1379	+	
1380	-	
1381	rac	
1382	+	
1383	-	
1384	rac	
1385	+	
1386	-	
1387	rac	
1388	+	
1389	-	
1390	rac	
1391	+	
1392	-	
1393	rac	
1394	+	
1395	-	
1396	rac	
1397	+	
1398	-	
1399	rac	
1400	+	
1401	-	
1402	rac	
1403	+	
1404	-	
1405	rac	
1406	+	
1407	-	

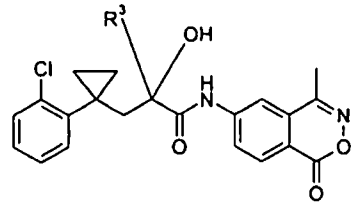
1408	rac	
1409	+	
1410	-	
1411	rac	
1412	+	
1413	-	
1414	rac	
1415	+	
1416	-	
1417	rac	
1418	+	
1419	-	
1420	rac	
1421	+	
1422	-	
1423	rac	
1424	+	
1425	-	
1426	rac	
1427	+	
1428	-	

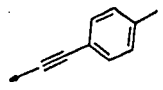
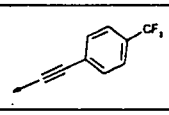
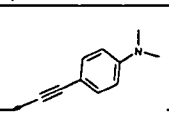
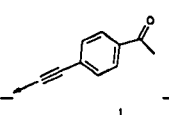
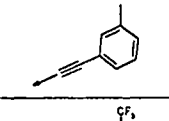
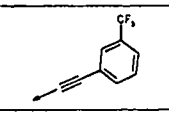
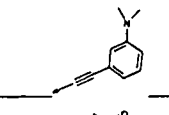
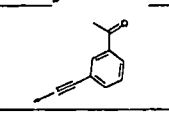
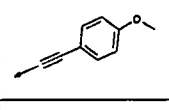
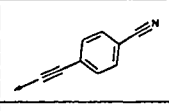
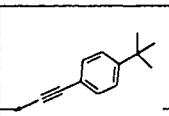
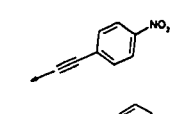
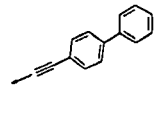
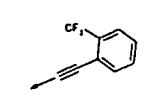
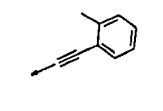
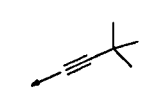
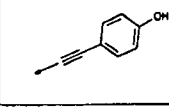
No.	Racemic or enantiomer	R3
1429	rac	
1430	-	
1431	+	
1432	rac	
1433	+	
1434	-	
1435	rac	
1436	+	
1437	-	
1438	rac	
1439	+	
1440	-	
1441	rac	
1442	+	
1443	-	
1444	rac	
1445	+	
1446	-	
1447	rac	
1448	+	
1449	-	
1450	rac	
1451	+	
1452	-	
1453	rac	
1454	+	
1455	-	

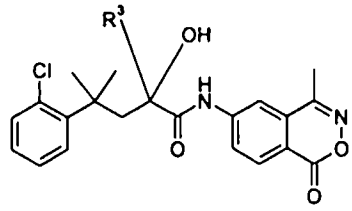


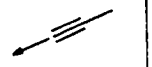
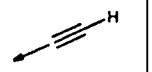
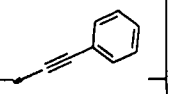
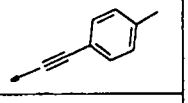
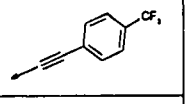
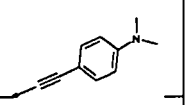
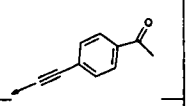
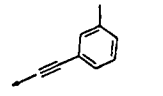
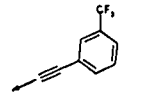
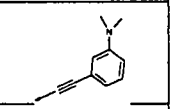
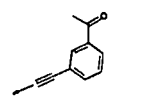
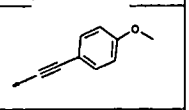
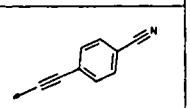
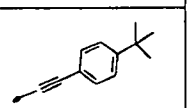
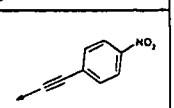
1456	rac	
1457	+	
1458	-	
1459	rac	
1460	+	
1461	-	
1462	rac	
1463	+	
1464	-	
1465	rac	
1466	+	
1467	-	
1468	rac	
1469	+	
1470	-	
1471	rac	
1472	+	
1473	-	
1474	rac	
1475	+	
1476	-	
1477	rac	
1478	+	
1479	-	
1480	rac	
1481	+	
1482	-	
1483	rac	
1484	+	
1485	-	
1486	rac	
1487	+	
1488	-	
1489	rac	
1490	+	
1491	-	

No.	Racemic or enantiomer	R3
1492	rac	
1493	-	
1494	+	
1495	rac	
1496	+	
1497	-	
1498	rac	
1499	+	
1500	-	
1501	rac	
1502	+	
1503	-	

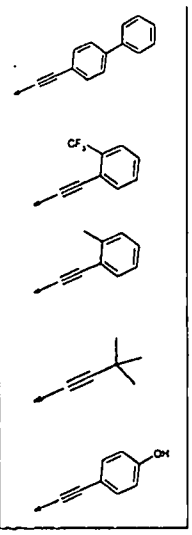


1504	rac	
1505	+	
1506	-	
1507	rac	
1508	+	
1509	-	
1510	rac	
1511	+	
1512	-	
1513	rac	
1514	+	
1515	-	
1516	rac	
1517	+	
1518	-	
1519	rac	
1520	+	
1521	-	
1522	rac	
1523	+	
1524	-	
1525	rac	
1526	+	
1527	-	
1528	rac	
1529	+	
1530	-	
1531	rac	
1532	+	
1533	-	
1534	rac	
1535	+	
1536	-	
1537	rac	
1538	+	
1539	-	
1540	rac	
1541	+	
1542	-	
1543	rac	
1544	+	
1545	-	
1546	rac	
1547	+	
1548	-	
1549	rac	
1550	+	
1551	-	
1552	rac	
1553	+	
1554	-	

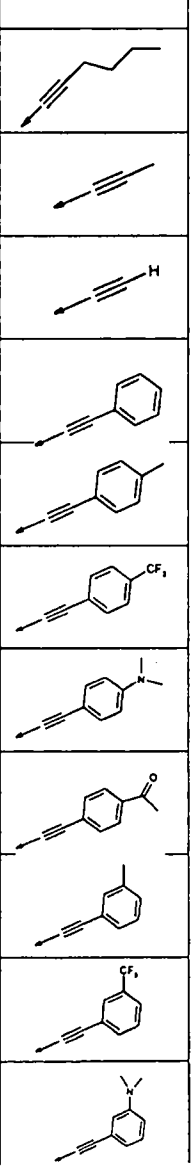


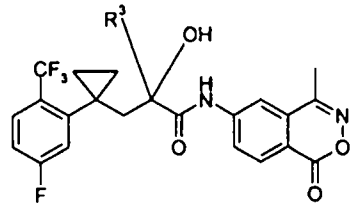
No.	Racemic or enantiomer oder Enantiomer	R3
1555	rac	
1556	-	
1557	+	
1558	rac	
1559	+	
1560	-	
1561	rac	
1562	+	
1563	-	
1564	rac	
1565	+	
1566	-	
1567	rac	
1568	+	
1569	-	
1570	rac	
1571	+	
1572	-	
1573	rac	
1574	+	
1575	-	
1576	rac	
1577	+	
1578	-	
1579	rac	
1580	+	
1581	-	
1582	rac	
1583	+	
1584	-	
1585	rac	
1586	+	
1587	-	
1588	rac	
1589	+	
1590	-	
1591	rac	
1592	+	
1593	-	
1594	rac	
1595	+	
1596	-	
1597	rac	
1598	+	
1599	-	
1600	rac	
1601	+	
1602	-	

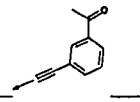
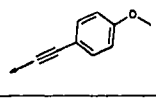
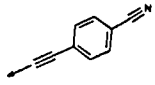
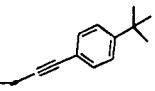
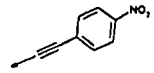
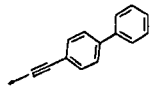
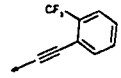
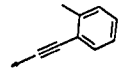
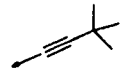
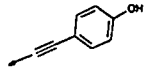
1603	rac
1604	+
1605	-
1606	rac
1607	+
1608	-
1609	rac
1610	+
1611	-
1612	rac
1613	+
1614	-
1615	rac
1616	+
1617	-

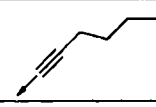
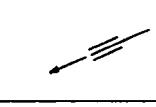
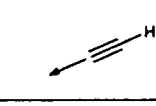
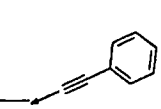
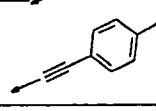
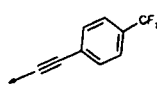


No.	Racemic or enantiomer	R3
1618	rac	
1619	-	
1620	+	
1621	rac	
1622	+	
1623	-	
1624	rac	
1625	+	
1626	-	
1627	rac	
1628	+	
1629	-	
1630	rac	
1631	+	
1632	-	
1633	rac	
1634	+	
1635	-	
1636	rac	
1637	+	
1638	-	
1639	rac	
1640	+	
1641	-	
1642	rac	
1643	+	
1644	-	
1645	rac	
1646	+	
1647	-	
1648	rac	
1649	+	
1650	-	





1651	rac	
1652	+	
1653	-	
1654	rac	
1655	+	
1656	-	
1657	rac	
1658	+	
1659	-	
1660	rac	
1661	+	
1662	-	
1663	rac	
1664	+	
1665	-	
1666	rac	
1667	+	
1668	-	
1669	rac	
1670	+	
1671	-	
1672	rac	
1673	+	
1674	-	
1675	rac	
1676	+	
1677	-	
1678	rac	
1679	+	
1680	-	

No.	Racemic or enantiomer	R3
1681	rac	
1682	-	
1683	+	
1684	rac	
1685	+	
1686	-	
1687	rac	
1688	+	
1689	-	
1690	rac	
1691	+	
1692	-	
1693	rac	
1694	+	
1695	-	
1696	rac	
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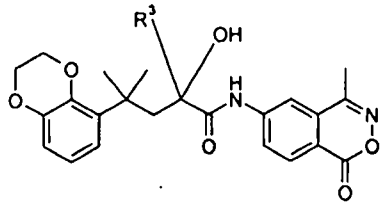
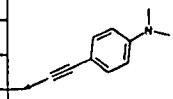
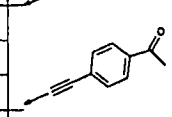
1698	-	



1699	rac	
1700	+	
1701	-	
1702	rac	
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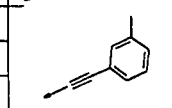
1704	-	
1705	rac	
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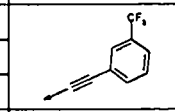
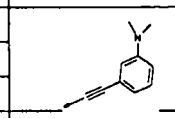
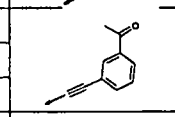
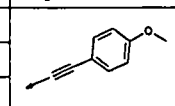
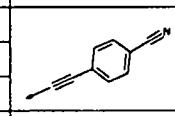
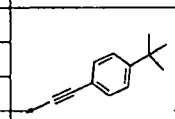
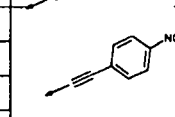
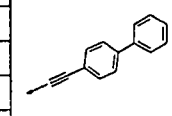
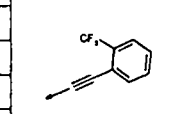
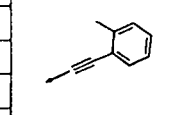
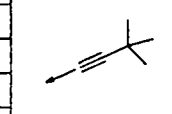
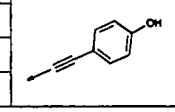
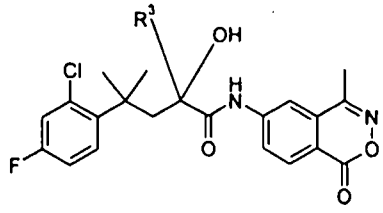
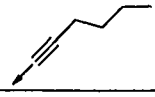
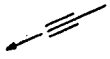
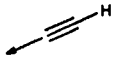
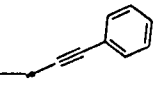
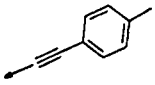
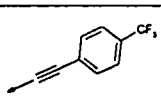
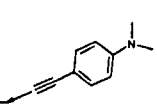
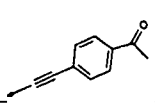
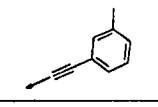
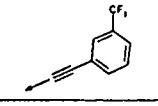
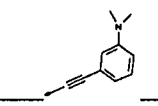
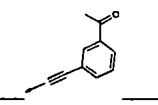
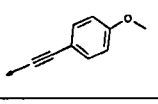
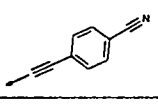
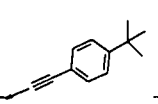
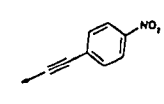
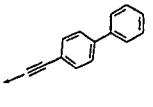
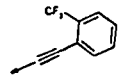
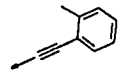
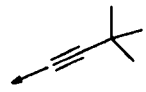
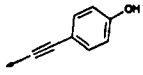
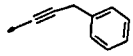
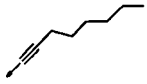
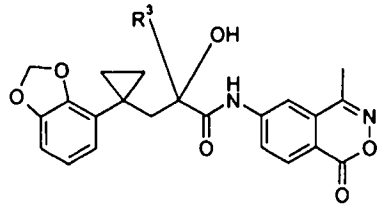
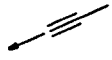
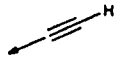
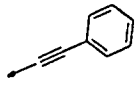
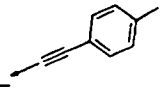
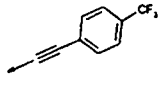
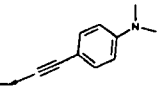
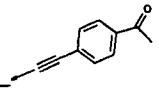
1708	rac	
1709	+	
1710	-	
1711	rac	
1712	+	
1713	-	
1714	rac	
1715	+	
1716	-	
1717	rac	
1718	+	
1719	-	
1720	rac	
1721	+	
1722	-	
1723	rac	
1724	+	
1725	-	
1726	rac	
1727	+	
1728	-	
1729	rac	
1730	+	
1731	-	
1732	rac	
1733	+	
1734	-	
1735	rac	
1736	+	
1737	-	
1738	rac	
1739	+	
1740	-	
1741	rac	
1742	+	
1743	-	



No.	Racemic or enantiomer	R3
1744	rac	
1745	-	
1746	+	
1747	rac	
1748	+	
1749	-	
1750	rac	
1751	+	
1752	-	
1753	rac	
1754	+	
1755	-	
1756	rac	
1757	+	
1758	-	
1759	rac	
1760	+	
1761	-	
1762	rac	
1763	+	
1764	-	
1765	rac	
1766	+	
1767	-	
1768	rac	
1769	+	
1770	-	
1771	rac	
1772	+	
1773	-	
1774	rac	
1775	+	
1776	-	
1777	rac	
1778	+	
1779	-	
1780	rac	
1781	+	
1782	-	
1783	rac	
1784	+	
1785	-	
1786	rac	
1787	+	
1788	-	
1789	rac	
1790	+	
1791	-	
1792	rac	
1793	+	
1794	-	

1795	rac	
1796	+	
1797	-	
1798	rac	
1799	+	
1800	-	
1801	rac	
1802	+	
1803	-	
1804	rac	
1805	+	
1806	-	
1807	rac	
1808	+	
1809	-	
1810	rac	
1811	+	
1812	-	



No.	Racemic or enantiomer	R3
1813	rac	
1814	-	
1815	+	
1816	rac	
1817	+	
1818	-	
1819	rac	
1820	+	
1821	-	
1822	rac	
1823	+	
1824	-	
1825	rac	
1826	+	
1827	-	
1828	rac	
1829	+	
1830	-	
1831	rac	
1832	+	
1833	-	
1834	rac	
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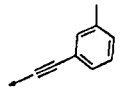
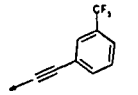
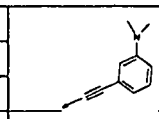
1837	rac	
1838	+	
1839	-	
1840	rac	
1841	+	
1842	-	

60

1843	rac	
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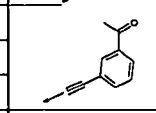
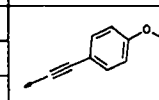
1845	-	
1846	rac	
1847	+	
1848	-	
1849	rac	
1850	+	
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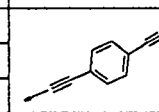
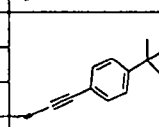
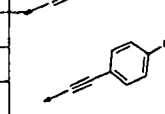
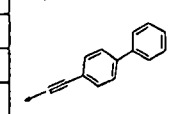
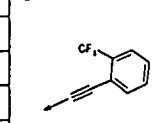
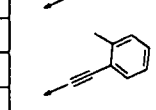
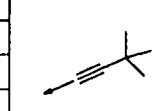
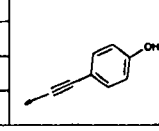
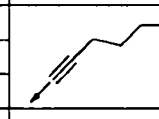
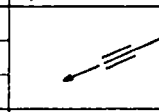
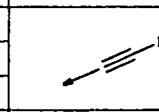
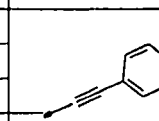
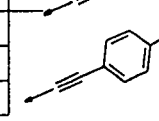
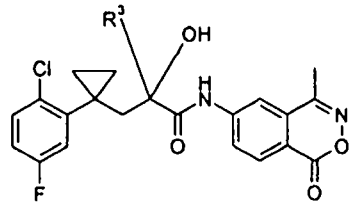
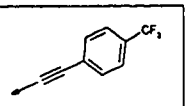
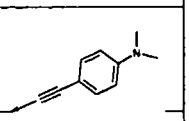
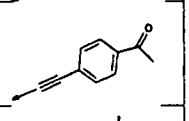
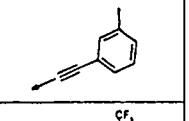
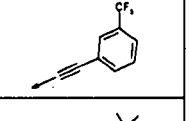
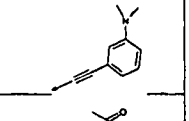
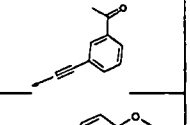
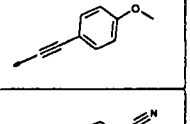
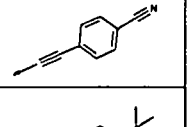
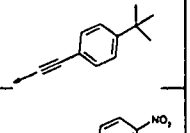
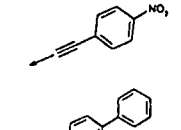
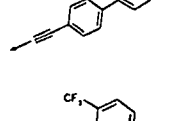
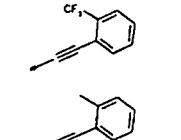
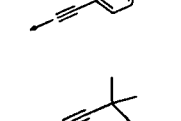
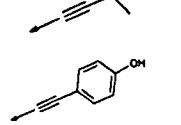
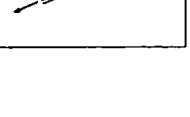
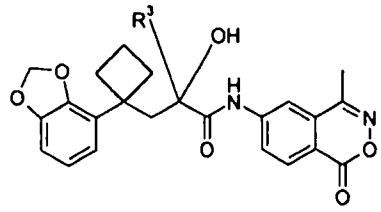
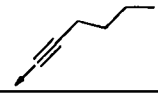
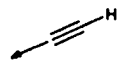
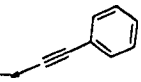
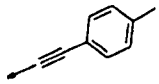
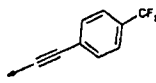
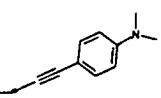
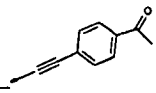
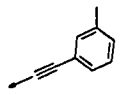
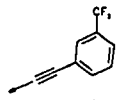
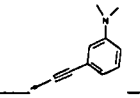
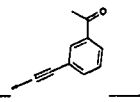
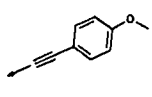
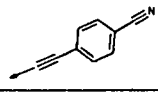
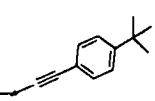
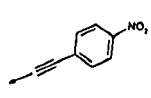
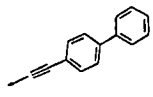
1852	rac	
1853	+	
1854	-	
1855	rac	
1856	+	
1857	-	
1858	rac	
1859	+	
1860	-	
1861	rac	
1862	+	
1863	-	
1864	rac	
1865	+	
1866	-	
1867	rac	
1868	+	
1869	-	
1870	rac	
1871	+	
1872	-	
1873	rac	
1874	+	
1875	-	

No.	Racemic or enantiomer	R3
1876	rac	
1877	-	
1878	+	
1879	rac	
1880	+	
1881	-	
1882	rac	
1883	+	
1884	-	
1885	rac	
1886	+	
1887	-	
1888	rac	
1889	+	
1890	-	

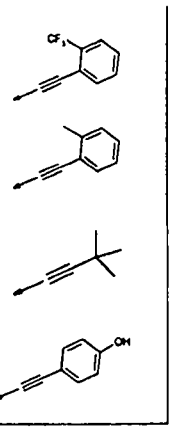


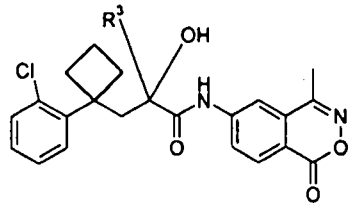
1891	rac	
1892	+	
1893	-	
1894	rac	
1895	+	
1896	-	
1897	rac	
1898	+	
1899	-	
1900	rac	
1901	+	
1902	-	
1903	rac	
1904	+	
1905	-	
1906	rac	
1907	+	
1908	-	
1909	rac	
1910	+	
1911	-	
1912	rac	
1913	+	
1914	-	
1915	rac	
1916	+	
1917	-	
1918	rac	
1919	+	
1920	-	
1921	rac	
1922	+	
1923	-	
1924	rac	
1925	+	
1926	-	
1927	rac	
1928	+	
1929	-	
1930	rac	
1931	+	
1932	-	
1933	rac	
1934	+	
1935	-	
1936	rac	
1937	+	
1938	-	



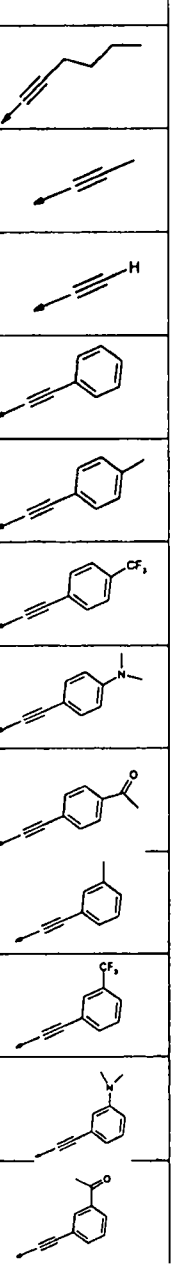
No.	Racemic or enantiomer	R3
1939	rac	
1940	-	
1941	+	
1942	rac	
1943	+	
1944	-	
1945	rac	
1946	+	
1947	-	
1948	rac	
1949	+	
1950	-	
1951	rac	
1952	+	
1953	-	
1954	rac	
1955	+	
1956	-	
1957	rac	
1958	+	
1959	-	
1960	rac	
1961	+	
1962	-	
1963	rac	
1964	+	
1965	-	
1966	rac	
1967	+	
1968	-	
1969	rac	
1970	+	
1971	-	
1972	rac	
1973	+	
1974	-	
1975	rac	
1976	+	
1977	-	
1978	rac	
1979	+	
1980	-	
1981	rac	
1982	+	
1983	-	
1984	rac	
1985	+	
1986	-	
1987	rac	
1988	+	
1989	-	

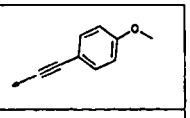
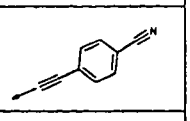
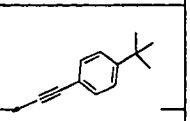
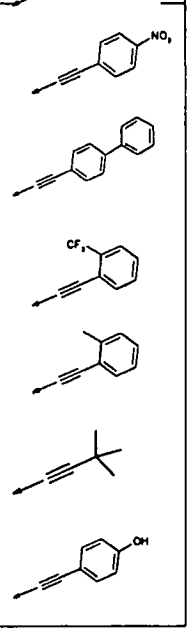
1990	rac
1991	+
1992	-
1993	rac
1994	+
1995	-
1996	rac
1997	+
1998	-
1999	rac
2000	+
2001	-

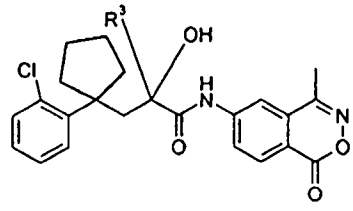


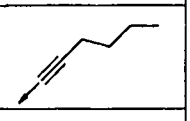
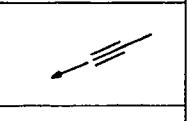
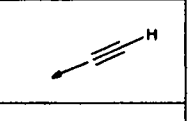
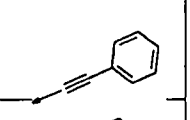
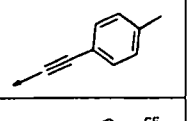
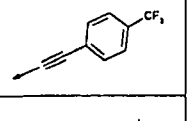
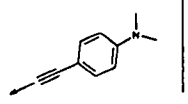


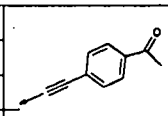
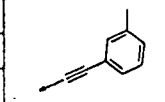
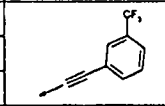
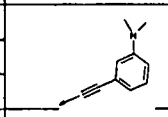
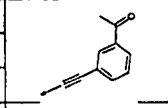
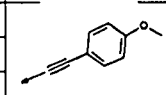
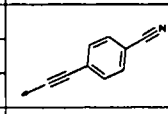
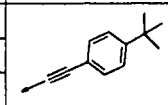
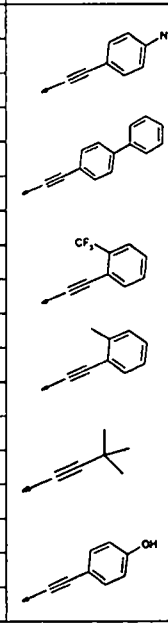
No.	Racemic or enantiomer	R3
2002	rac	
2003	-	
2004	+	
2005	rac	
2006	+	
2007	-	
2008	rac	
2009	+	
2010	-	
2011	rac	
2012	+	
2013	-	
2014	rac	
2015	+	
2016	-	
2017	rac	
2018	+	
2019	-	
2020	rac	
2021	+	
2022	-	
2023	rac	
2024	+	
2025	-	
2026	rac	
2027	+	
2028	-	
2029	rac	
2030	+	
2031	-	
2032	rac	
2033	+	
2034	-	
2035	rac	
2036	+	
2037	-	

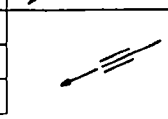


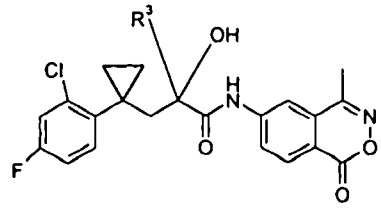
2038	rac	
2039	+	
2040	-	
2041	rac	
2042	+	
2043	-	
2044	rac	
2045	+	
2046	-	
2047	rac	
2048	+	
2049	-	
2050	rac	
2051	+	
2052	-	
2053	rac	
2054	+	
2055	-	
2056	rac	
2057	+	
2058	-	
2059	rac	
2060	+	
2061	-	
2062	rac	
2063	+	
2064	-	

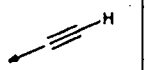
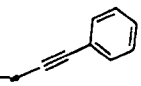
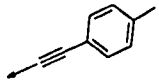
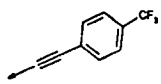
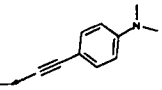
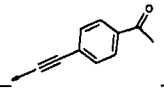
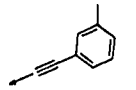
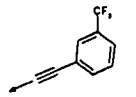
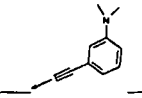
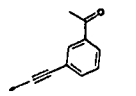
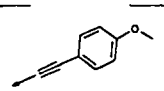
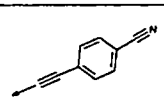
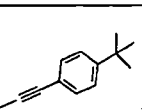
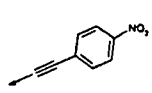
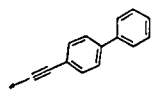
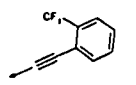
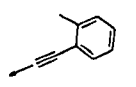


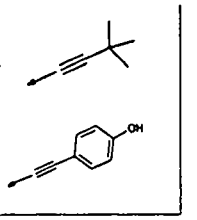
No.	Racemic or enantiomer	R3
2065	rac	
2066	-	
2067	+	
2068	rac	
2069	+	
2070	-	
2071	rac	
2072	+	
2073	-	
2074	rac	
2075	+	
2076	-	
2077	rac	
2078	+	
2079	-	
2080	rac	
2081	+	
2082	-	
2083	rac	
2084	+	
2085	-	

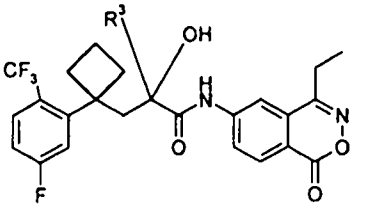
2086	rac	
2087	+	
2088	-	
2089	rac	
2090	+	
2091	-	
2092	rac	
2093	+	
2094	-	
2095	rac	
2096	+	
2097	-	
2098	rac	
2099	+	
2100	-	
2101	rac	
2102	+	
2103	-	
2104	rac	
2105	+	
2106	-	
2107	rac	
2108	+	
2109	-	
2110	rac	
2111	+	
2112	-	
2113	rac	
2114	+	
2115	-	
2116	rac	
2117	+	
2118	-	
2119	rac	
2120	+	
2121	-	
2122	rac	
2123	+	
2124	-	
2125	rac	
2126	+	
2127	-	

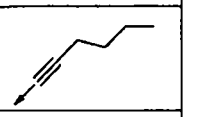
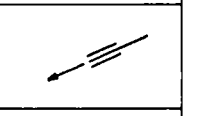
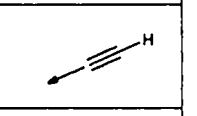
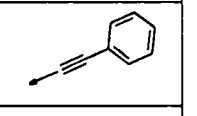
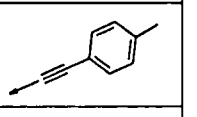
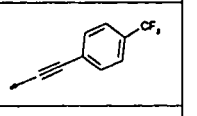
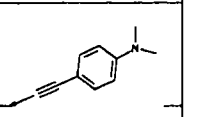
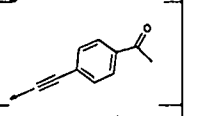
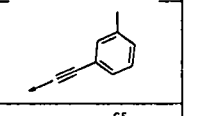
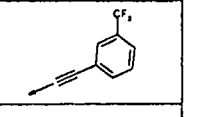
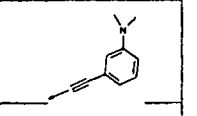
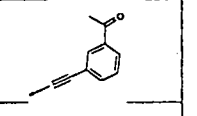
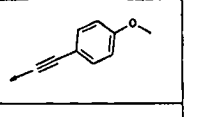
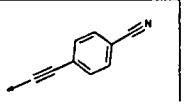
No.	Racemic or enantiomer	R3
2128	rac	
2129	-	
2130	+	
2131	rac	
2132	+	
2133	-	

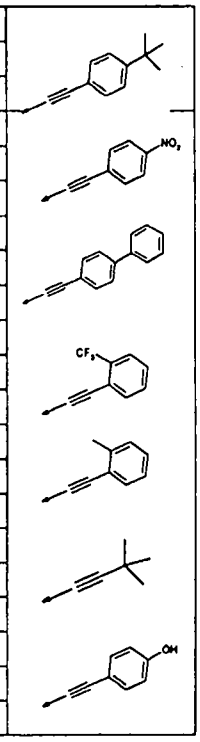


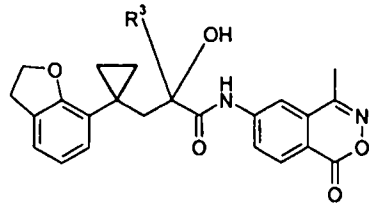
2134	rac	
2135	+	
2136	-	
2137	rac	
2138	+	
2139	-	
2140	rac	
2141	+	
2142	-	
2143	rac	
2144	+	
2145	-	
2146	rac	
2147	+	
2148	-	
2149	rac	
2150	+	
2151	-	
2152	rac	
2153	+	
2154	-	
2155	rac	
2156	+	
2157	-	
2158	rac	
2159	+	
2160	-	
2161	rac	
2163	+	
2163	-	
2164	rac	
2165	+	
2166	-	
2167	rac	
2168	+	
2169	-	
2170	rac	
2171	+	
2172	-	
2173	rac	
2174	+	
2175	-	
2176	rac	
2177	+	
2178	-	
2179	rac	
2180	+	
2181	-	
2182	rac	
2183	+	
2184	-	

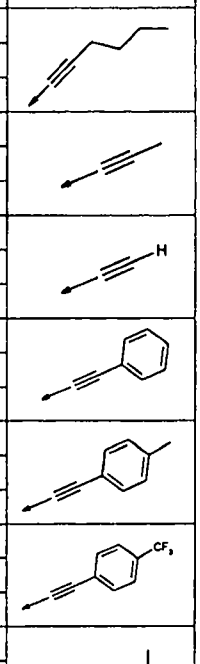
2185	rac	
2186	+	
2187	-	
2188	rac	
2189	+	
2190	-	

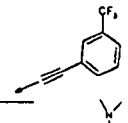
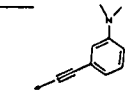
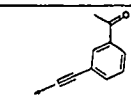
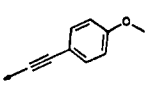
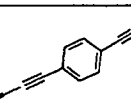
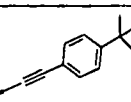
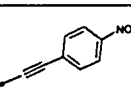
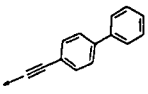
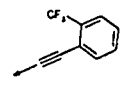
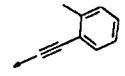
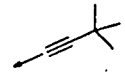
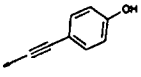


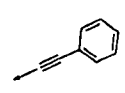
No.	Racemic or enantiomer	R3
2191	rac	
2192	-	
2193	+	
2194	rac	
2195	+	
2196	-	
2197	rac	
2198	+	
2199	-	
2200	rac	
2201	+	
2202	-	
2203	rac	
2204	+	
2205	-	
2206	rac	
2207	+	
2208	-	
2209	rac	
2210	+	
2211	-	
2212	rac	
2213	+	
2214	-	
2215	rac	
2216	+	
2217	-	
2218	rac	
2219	+	
2220	-	
2221	rac	
2222	+	
2223	-	
2224	rac	
2225	+	
2226	-	
2227	rac	
2228	+	
2229	-	
2230	rac	
2231	+	
2232	-	

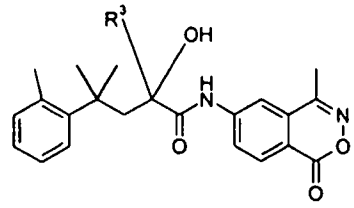
2233	rac	
2234	+	
2235	-	
2236	rac	
2237	+	
2238	-	
2239	rac	
2240	+	
2241	-	
2242	rac	
2243	+	
2244	-	
2245	rac	
2246	+	
2247	-	
2248	rac	
2249	+	
2250	-	
2251	rac	
2252	+	
2253	-	

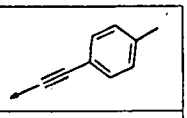
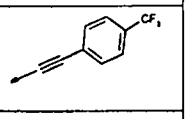
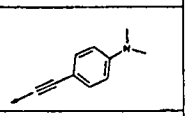
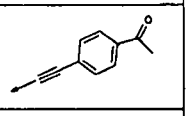
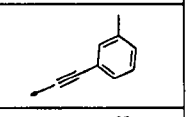
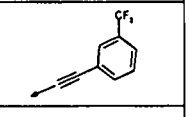
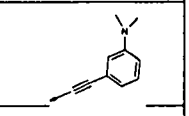
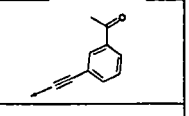
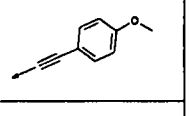
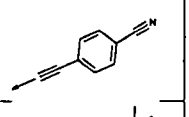
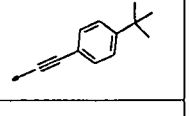
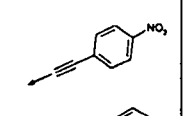
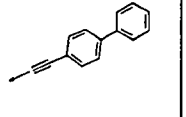
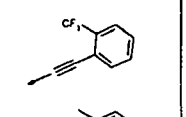
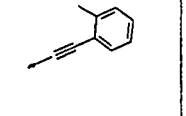
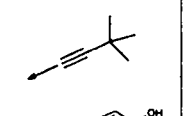
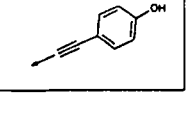


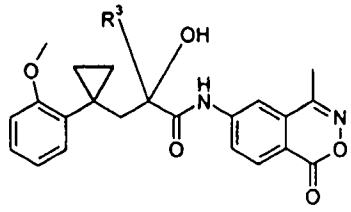
No.	Racemic or enantiomer	R3
2254	rac	
2255	-	
2256	+	
2257	rac	
2258	+	
2259	-	
2260	rac	
2261	+	
2262	-	
2263	rac	
2264	+	
2265	-	
2266	rac	
2267	+	
2268	-	
2269	rac	
2270	+	
2271	-	
2272	rac	
2273	+	
2274	-	
2273	rac	
2276	+	
2277	-	
2278	rac	
2279	+	
2280	-	

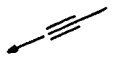
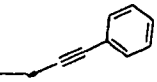
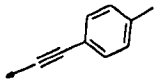
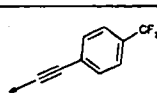
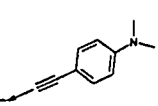
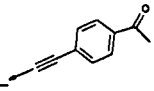
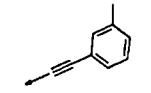
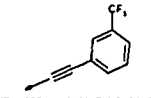
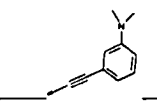
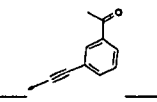
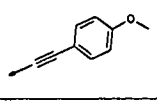
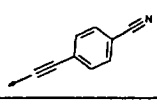
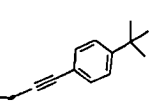
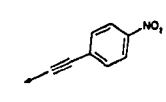
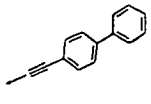
2281	rac	
2282	+	
2283	-	
2284	rac	
2285	+	
2286	-	
2287	rac	
2288	+	
2289	-	
2290	rac	
2291	+	
2292	-	
2293	rac	
2294	+	
2295	-	
2296	rac	
2297	+	
2298	-	
2299	rac	
2300	+	
2301	-	
2302	rac	
2303	+	
2304	-	
2305	rac	
2306	+	
2307	-	
2308	rac	
2309	+	
2310	-	
2311	rac	
2312	+	
2313	-	
2314	rac	
2315	+	
2316	-	

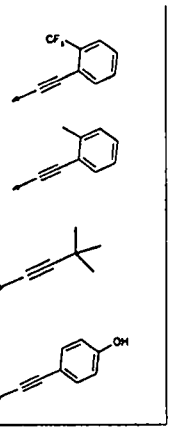
No.	Racemic or enantiomer	R3
2317	rac	
2318	-	
2319	+	
2320	rac	
2321	+	
2322	-	
2323	rac	
2324	+	
2325	-	
2326	rac	
2327	+	
2328	-	

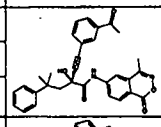
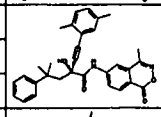
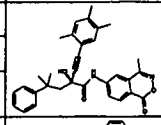
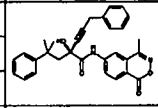
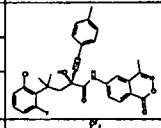
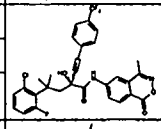
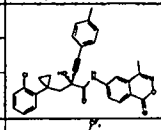
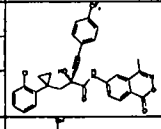
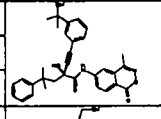
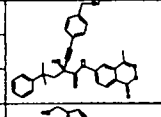
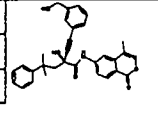


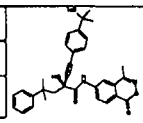
2329	rac	
2330	+	
2331	-	
2332	rac	
2333	+	
2334	-	
2335	rac	
2336	+	
2337	-	
2338	rac	
2339	+	
2340	-	
2341	rac	
2342	+	
2343	-	
2344	rac	
2345	+	
2346	-	
2347	rac	
2348	+	
2349	-	
2350	rac	
2351	+	
2652	-	
2353	rac	
2354	+	
2355	-	
2356	rac	
2357	+	
2358	-	
2359	rac	
2360	+	
2361	-	
2362	rac	
2363	+	
2364	-	
2365	rac	
2366	+	
2367	-	
2368	rac	
2369	+	
2370	-	
2371	rac	
2372	+	
2373	-	
2374	rac	
2375	+	
2376	-	
2377	rac	
2378	+	
2379	-	



No.	Racemic or enantiomer	R3
2380	rac	
2381	-	
2382	+	
2383	rac	
2384	+	
2385	-	
2386	rac	
2387	+	
2388	-	
2389	rac	
2390	+	
2391	-	
2392	rac	
2393	+	
2394	-	
2395	rac	
2396	+	
2397	-	
2398	rac	
2399	+	
2400	-	
2401	rac	
2402	+	
2403	-	
2404	rac	
2405	+	
2406	-	
2407	rac	
2408	+	
2409	-	
2410	rac	
2411	+	
2412	-	
2413	rac	
2414	+	
2415	-	
2416	rac	
2417	+	
2418	-	
2419	rac	
2420	+	
2421	-	
2422	rac	
2423	+	
2424	-	
2425	rac	
2426	+	
2427	-	
2428	rac	
2429	+	
2430	-	

2431	rac	
2432	+	
2433	-	
2434	rac	
2435	+	
2436	-	
2437	rac	
2438	+	
2439	-	
2440	rac	
2441	+	
2442	-	

No.	Racemic or enantiomer	Structure
2443	rac	
2444	-	
2445	+	
2446	rac	
2447	+	
2448	-	
2449	rac	
2450	+	
2451	-	
2452	rac	
2453	+	
2454	-	
2455	rac	
2456	+	
2457	-	
2458	rac	
2459	+	
2460	-	
2461	rac	
2462	+	
2463	-	
2464	rac	
2465	+	
2466	-	
2467	rac	
2468	+	
2469	-	
2470	rac	
2471	+	
2472	-	
2473	rac	
2474	+	
2475	-	

2476	rac	
2477	+	
2478	-	

Biological characterization of the compounds according to the invention

Progesterone receptor modulators can be identified with the aid of simple methods, test programmes known to the skilled person. It is possible for this purpose for example to incubate a compound to be tested together with a progestogen in a test system for progesterone receptors and to check whether the effect mediated by progesterone is altered in the presence of the modulator in this test system.

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

Progesterone receptor-binding assay

Measurement of the receptor binding affinity:

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

The tracer and increasing concentrations of the compound to be tested (competitor) were coincubated at 0-4°C for 18 h with the receptor-containing cytosol fraction. After removal of unbound tracer with carbon-dextran suspension, the receptor-bound tracer content was measured for each concentration, and the IC_{50} was determined from the concentration series. The relative molar binding affinity (RBA) was calculated as ratio of the IC_{50} values for reference substance and compound to be tested (x 100%) (RBA of the reference substance = 100%).

The following incubation conditions were chosen for the receptor types:

Progesterone receptor:

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

Glucocorticoid receptor:

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

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

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

Antagonism at the PR-B progesterone receptor

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

Agonism on the PR-B progesterone receptor

The transactivation assay is carried out 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 Acticity	
	IC_{50} [nM]	Efficacy [%]	EC_{50} [nM]	Efficacy [%]
5	0,2	86	0,2	10
14	6	53	7	35
16	0,7	82	0,5	13
17b	0,03	88	n.b.	7
18	0,2	89	n.b.	8
24	2	100		0
35	2	100		0

Dosage

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

Satisfactory results are generally to be expected in the treatment of the indications mentioned hereinbefore when the daily doses cover a range from 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, of leiomyomas of the uterus and dysfunctional bleeding and for use in fertility control and for hormone replacement therapy are from 50 μg to

500 mg per day, depending on the age and constitution of the patient, it being possible to administer the necessary daily dose by single or multiple administration.

The dosage range for the compounds according to the invention for the treatment of breast carcinomas is 10 mg to 1000 mg per day.

The pharmaceutical products based on the novel compounds are formulated in a manner known per se by processing the active ingredient with the carrier substances, fillers, substances influencing disintegration, binders, humectants, lubricants, absorbents, diluents, masking flavours, colorants, etc. which are used in pharmaceutical technology, and converting into the desired administration form. Reference should be made in this connection to Remington's Pharmaceutical Sciences, 15th ed. Mack Publishing Company, Easton, Pennsylvania (1980).

Suitable for oral administration are in particular tablets, film-coated tablets, sugar-coated tablets, capsules, pills, powders, granules, pastilles, suspensions, emulsions or solutions.

Preparations for injection and infusion are possible for parenteral administration.

Appropriately prepared crystal suspensions can be used for intraarticular injection.

Aqueous and oily solutions for injection or suspensions and corresponding depot preparations can be used for intramuscular injection.

For rectal administration, the novel compounds can be used in the form of suppositories, capsules, solutions (e.g. in the form of enemas) and ointments, both for systemic and for local therapy.
Furthermore, compositions for vaginal use may also be mentioned as preparation.

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

Patches are possible for transdermal administration, and formulations in gels, ointments, fatty ointments, creams, pastes, dusting powders, milk and tinctures are possible for topical application. The dosage of the compounds of the general formula I

in these preparations should be 0.01% - 20% in order to achieve an adequate pharmacological effect.

Corresponding tablets can be obtained for example by mixing active ingredient with known excipients, for example inert diluents such as dextrose, sugar, sorbitol, mannitol, polyvinylpyrrolidone, disintegrants such as maize starch or alginic acid, binders such as starch or gelatin, lubricants such as magnesium stearate or talc and/or means to achieve a depot effect such as carboxypolymethylene, carboxymethylcellulose, cellulose acetate phthalate or polyvinyl acetate. The tablets may also consist of a plurality of layers.

Correspondingly, coated tablets can be produced by coating cores produced in analogy to the tablets with compositions normally used in tablet coatings, for example polyvinylpyrrolidone or shellac, gum arabic, talc, titanium oxide or sugar. The tablet covering may in this case also consist of a plurality of layers, it being possible to use the excipients mentioned above for tablets.

Solutions or suspensions of the compounds according to the invention of the general formula I may additionally comprise taste-improving agents such as saccharin, cyclamate or sugar, and, for example, flavourings such as vanillin or orange extract. They may additionally comprise suspending excipients such as sodium carboxymethylcellulose or preservatives such as p-hydroxybenzoates.

Capsules comprising the compounds of the general formula I can be produced for example by mixing the compound(s) of the general formula I with an inert carrier such as lactose or sorbitol and encapsulating it in gelatin capsules.

Suitable suppositories can be produced for example by mixing with carriers intended for this purpose, such as neutral fats or polyethylene glycol or derivatives.

The compounds according to the invention of the general formula (I) or their pharmaceutically acceptable salts can be used, because of their antagonistic or partial agonistic activity, for producing a medicament, in particular for the treatment and prophylaxis of gynaecological disorders such as endometriosis, leiomyomas of the uterus, dysfunctional bleeding and dysmenorrhoea. They can furthermore be employed to counteract hormonal irregularities, for inducing menstruation and alone or in

combination with prostaglandins and/or oxytocin to induce labour.

The compounds according to the invention of the general formula (I) or their pharmaceutically acceptable salts are furthermore suitable for producing products for female contraception (see also WO 93/23020, WO 93/21927).
The compounds according to the invention or their pharmaceutically acceptable salts can additionally be employed alone or in combination with a selective estrogen receptor modulator (SERM) for female hormone replacement therapy.

In addition, the said compounds have an antiproliferative effect in hormone-dependent tumours. They are therefore suitable for the therapy of hormone-dependent carcinomas such as, for example, for breast, prostate and endometrial carcinomas.

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

The compounds according to the invention, having antagonistic or partially agonistic activity, of the general formula (I) or their pharmaceutically acceptable salts can also be used in combination with compounds having antiestrogenic activity (estrogen receptor antagonists or aromatase inhibitors) or selective estrogen receptor modulators (SERM) for producing pharmaceutical products for the treatment of hormone-dependent tumours. The compounds according to the invention can likewise be used in combination with SERMs or an antiestrogen (estrogen receptor antagonist or aromatase inhibitor) for the treatment of endometriosis or of leiomyomas of the uterus. In the treatment of hormone-dependent tumours 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 the sequential administration, preferably the antiestrogen (estrogen receptor antagonists or aromatase inhibitors) or SERM is administered first and subsequently the progesterone receptor modulator is administered.

Suitable for combination with the non-steroidal progesterone receptor modulators according to the invention in this connection are for example the following antiestrogens (estrogen receptor antagonists or aromatase inhibitors) or SERMs:
tamoxifen, 5-(4-{5-[(RS)-(4,4,5,5,5-pentafluoropentyl)sulphinyl]pentyloxy}phenyl)-6-

phenyl-8,9-dihydro-7H-benzocyclohepten-2-ol (WO 00/03979), ICI 182 780 (7alpha-[9-(4,4,5,5-pentafluoropentylsulphinyl)nonyl]estra-1,3,5(10)-triene-3,17beta-diol), 11beta-fluoro-7alpha-[5-(methyl{3-[(4,4,5,5,5-pentafluoropentyl)sulphanyl]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-3,17-beta-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), clomifen, raloxifen, and further compounds having antiestrogenic activity, and aromatase inhibitors such as, for example, fadrozole, formestane, letrozole, anastrozole or atamestane.

Finally, the present invention also relates to the use of the compounds of the general formula I, where appropriate together with an antiestrogen or SERM, for producing a medicament.

The present invention further relates to pharmaceutical compositions which comprise at least one compound according to the invention, where appropriate in the form of a pharmaceutically/pharmacologically acceptable salt, without or together with pharmaceutically acceptable excipients and/or carriers.

These pharmaceutical compositions and medicaments may be intended for oral, rectal, vaginal, subcutaneous, percutaneous, intravenous or intramuscular administration. Besides conventional carriers and/or diluents, they comprise at least one compound according to the invention.

The medicaments of the invention are produced with the conventional solid or liquid carriers or diluents and the excipients normally used in pharmaceutical technology appropriate for the desired mode of administration with a suitable dosage in a known manner. The preferred preparations consist of a dosage suitable for oral administration. Examples of such dosage forms are tablets, film-coated tablets, sugar-coated tablets, capsules, pills, powders, solutions or suspensions or else depot forms.

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

Also suitable are parenteral preparations such as solutions for injection. Further

preparations which may also be mentioned are for example suppositories and compositions for vaginal use.

The following examples serve to illustrate the subject-matter of the invention in more detail without wishing to restrict it thereto.

Preparation of the starting compounds 6-[4-(2-chloro-5-fluorophenyl)-4-methyl-2-oxovaleroylamino]-4-methyl-2,3-benzoxazin-1-one, 6-[4-(2-chloro-4-fluorophenyl)-4-methyl-2-oxovaleroylamino]-4-methyl-2,3-benzoxazin-1-one and 6-{3-[1-(2-chlorophenyl)cyclopentyl]-2-oxopropionylamino}-4-methyl-2,3-benzoxazin-1-one has been described in the patent US 2002/0077356, the compound 6-[4-(2,3-dihydro-7-benzofuranyl)-4-methyl-2-oxopentanoylamino]-4-methyl-2,3-benzoxazinone in US patent 6,323,199B1 (example 87 therein), the compound 6-(4-methyl-4-phenyl-2-oxovaleroylamino)-4-methyl-2,3-benzoxazin-1-one in the patent WO 199854159 and the compound 6-[3-[1-(2-fluoro-5-trifluoromethylphenyl)cyclopropyl]-2-oxopropionylamino]-4-methyl-2,3-benzoxazin-1-one in the patent WO 200375915.

General methods

1-(Benzo[1,3]dioxol-4-yl)-1-methylethanol

57.2 ml of methyl magnesium chloride solution (3M in THF) were added to 25.5 g of 4-acetylbenzo[1,3]dioxole in 375 ml of THF at RT under argon. The mixture was stirred at RT for 16 h and added to ice/2N hydrochloric acid. It was then extracted with ethyl acetate, and the organic phase was washed with water and brine and dried (Na_2SO_4). 27.89 g of 1-[benzo(1,3)dioxol-4-yl]-1-methylethanol were obtained as a brown oil.

^{1}H-NMR ($CDCl_3$, ppm) = 1.6 (s, 6H), 5.95 (s, 2H), 6.76 (dd, 1H), 6.82 (t, 1H), 6.91 (dd, 1H)

4-(Benzo[1,3]dioxol-4-yl)-4-methyl-2-oxopentanoic acid

47 ml of tin(IV) chloride were added to 9.5 g of 1-(benzo[1,3]dioxol-4-yl)-1-methylethanol and 14.2 g of ethyl 2-trimethylsilyloxyacrylate in 200 ml of dichloromethane at -70°C. After 15 minutes, the solution was added to potassium carbonate solution. After extraction with diethyl ether, the organic phase was washed with water, dried and evaporated.

14.4 g of the ethyl 4-(benzo[1,3]dioxol-4-yl)-4-methyl-2-oxopentanoate obtained in this way were stirred with 150 ml of 1 M sodium hydroxide and 300 ml of methanol at RT for 10 hours. The methanol was then removed in vacuo, and the remaining solution was extracted with diethyl ether. The aqueous phase was acidified with 1 M hydrochloric acid and extracted with diethyl ether. Drying and evaporation resulted in 11.1 g of

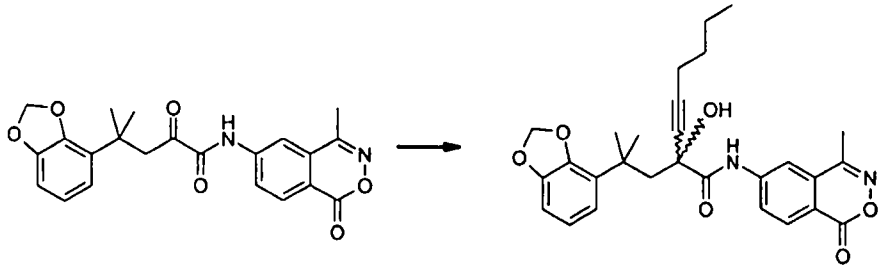
4-(benzo[1,3]dioxol-4-yl)-4-methyl-2-oxopentanoic acid as yellowish oil.
MS (ei) m/e: M^+ = 251

6-[4-(Benzo[1,3]dioxol-4-yl)-4-methyl-2-oxovaleroylamino]-4-methyl-2,3-benzoxazin-1-one

10 g of 4-(benzo[1,3]dioxol-4-yl)-4-methyl-2-oxopentanoic acid were dissolved in 125 ml of dimethylacetamide and, at -0°C under argon, 3.5 ml of thionyl chloride were added. After stirring at -3 to +3°C for 20 minutes, 7.6 g of 6-amino-4-methyl-2,3-benzoxazin-1-one (WO 00/32584) were added. The mixture was stirred at room temperature for 96 hours and, after addition of water, extracted with ethyl acetate, the organic phase was washed with water and dried (Na_2SO_4), and evaporation of the solvent and chromatography of the crude product on silica gel with hexane/ethyl acetate (100:0 -> 60:40) resulted in 6.56 g of 6-[4-(benzo[1,3]dioxol-4-yl)-4-methyl-2-oxovaleroylamino]-4-methyl-2,3-benzoxazin-1-one as a beige solid.
m.p. = 165-166°C, MS (ei) m/e: M^+ = 409

Synthesis examples

(-)-6-{2-[2-(2,3-(Methylenedioxy)phenyl)-2-methylpropyl]-2-hydroxyoct-3-ynoyl}-4-methyl-2,3-benzoxazin-1-one 1 and (+)-6-{2-[2-(2,3-(methylenedioxy)phenyl)-2-methylpropyl]-2-hydroxyoct-3-ynoyl}-4-methyl-2,3-benzoxazin-1-one 2

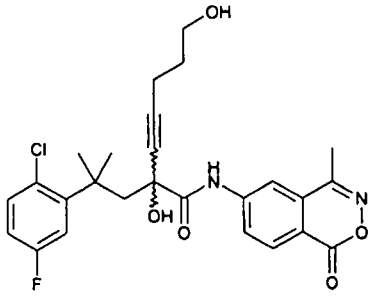


nBuLi (0.7 ml, 1.6M in hexane) was added to a solution of 1-hexyne (0.5 ml) in THF (4 ml) at -78°C. The mixture was stirred at -78°C for 20 min, 6-[4-(benzo[1,3]dioxol-4-yl)-4-methyl-2-oxovaleroylamino]-4-methyl-2,3-benzoxazin-1-one (192 mg) was added, and the mixture was stirred at -78°C for 4 h. Water was then added and the mixture was allowed to reach room temp. Extraction with ethyl acetate, washing with saturated sodium chloride solution, drying over sodium sulphate and purification by column chromatography on silica gel resulted in 82 mg of a white foam which was then converted by preparative chiral HPLC (Chiralpak AD 250 x 10 mm, eluent:

acetonitrile/water 55/45 v/v, flow rate 4.7 ml/min, temperature 40°C, retention times: 12.2 min (+)-enantiomer, 15.7 min (-)-enantiomer) into the compounds (-)-6-{2-[2-(2,3-(methylenedioxy)phenyl)-2-methylpropyl]-2-hydroxyoct-3-ynoyl}-4-methyl-2,3-benzoxazin-1-one (Example 1) and (+)-6-{2-[2-(2,3-(methylenedioxy)phenyl)-2-methylpropyl]-2-hydroxyoct-3-ynoyl}-4-methyl-2,3-benzoxazin-1-one (Example 2).

1H-NMR (ppm, $CDCl_3$, 400 MHz): 0.91 (t, J = 7.2 Hz, 3H, CH3), 1.32 – 1.49 (m, 4H), 1.55 (s, 3H), 1.58 (s, 3H), 2.17 (t, J = 7.2 Hz, 2H), 2.56 (s, 3H, CH3), 2.59 (d, J = 14.4 Hz, 1H), 2.74 (d, J = 14.8 Hz, 1H), 2.80 (s, 1H, OH), 5.94 – 5.96 (m, 2H), 6.46 – 6.49 (m, 1H), 6.64 (t, J = 7.8 Hz, 1H), 7.47 – 7.49 (m, 1H), 8.25 – 8.28 (m, 1H), 8.76 (s, 1H, NH). $C_{28}H_{30}N_2O_6$ (490.6):

rac-6-{2-[2-(2-Chloro-5-fluorophenyl)-2-methylpropyl]-2,7-dihydroxyhept-3-ynoyl}-4-methyl-2,3-benzoxazin-1-one 3

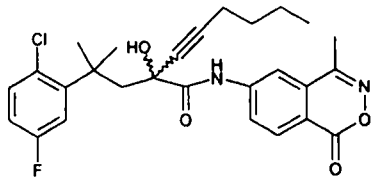


Stage A: Reaction of 5-(*tert*-butyldimethylsilyloxy)pent-1-yne (531 mg), nBuLi (0.7 ml, 1.6 M in hexane) and 6-[4-(2-chloro-5-fluorophenyl)-4-methyl-2-oxovaleroylamino]-4-methyl-2,3-benzoxazin-1-one (207 mg) at -78°C as described for Example 1 gave, after column chromatography on silica gel, a colourless oil (86 mg).

Stage B: The resulting oil was stirred in THF (3 ml) at room temp. under argon (3 h). Addition of water, extraction with ethyl acetate and washing with saturated brine were followed by drying with sodium sulphate. Purification by column chromatography on silica gel led to the title compound as a white foam (43 mg).

1H-NMR (ppm, $CDCl_3$, 400 MHz): 1.58 (s, 3H, Me), 1.59 (s, 3H, Me), 1.71 – 1.74 (m, 2H, CH_2), 2.2 – 2.3 (m, 2H), 2.56 (s, 3H, CH_3), 2.75 (d, J = 15.2 Hz, 1H, CH), 2.92 (d, J = 14.8 Hz, 1H, CH), 3.26 (s, 1H, OH), 3.74 – 3.78 (m, 2H), 6.67 – 6.78 (m, 1H), 7.09 – 7.19 (m, 2H), 7.66 – 7.69 (m, 2H), 8.20 – 8.21 (m, 1H), 8.27 – 8.29 (m, 1H), 8.99 (s, 1H, NH). $C_{26}H_{26}ClFN_2O_5$ (501.0): LC-MS: m/z = 501 [M + H^+].

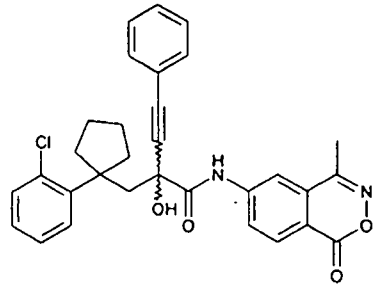
rac-6-{2-[2-(2-Chloro-5-fluorophenyl)-2-methylpropyl]-2-hydroxyoct-3-ynoyl}-4-methyl-2,3-benzoxazin-1-one 4



Reaction of 1-hexyne (0.6 ml), nBuLi (0.7 ml, 1.6 M in hexane) and 6-[4-(2-chloro-5-fluorophenyl)-4-methyl-2-oxovaleroylamino]-4-methyl-2,3-benzoxazin-1-one (207 mg) at -78°C as described for Example 1 gave, after column chromatography on silica gel and preparative thin-layer chromatography a viscous oil (12 mg).

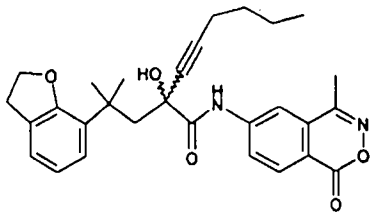
1H-NMR (ppm, $CDCl_3$, 400 MHz): 0.90 (t, J = 7.2 Hz, 3H, Me), 1.32 – 1.47 (m, 4H), 1.57 (s, 3H, Me), 1.62 (s, 3H, Me), 2.13 (t, J = 7.2 Hz, $CH_2C{\equiv}C$), 2.56 (s, 3H, Me), 2.81 – 2.95 (m, 3H), 6.68 – 6.71 (m, 1H), 7.11 – 7.17 (m, 2H), 7.56 – 7.58 (m, 1H), 8.21 (d, J = 2.0 Hz, 1H), 8.29 (d, J = 12.6 Hz, 1H), 8.73 (br. s., 1H, NH). $C_{27}H_{28}ClFN_2O_4$ (499.0): LC-MS: m/z = 499 [M + H^+].

rac-6-{2-[(2-Chlorophenyl)cyclopentyl]methyl-2-hydroxy-4-phenylbut-3-ynoyl-amino}-4-methyl-2,3-benzoxazin-1-one 5



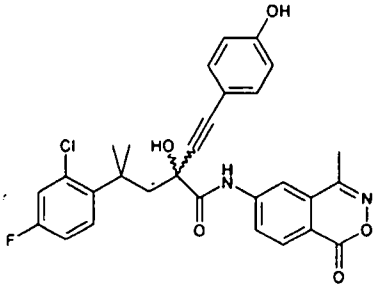
Lithiumphenylacetylide (0.65 ml, 1M in THF) was added to 6-{3-[1-(2-chlorophenyl)-cyclopentyl]-2-oxopropionylamino}-4-methyl-2,3-benzoxazin-1-one (110 mg) at -78°C and allowed to reach room temperature under argon during the night. Working up as described for Example 1 and column chromatography on silica gel resulted in the title compound as a foam (54 mg) after oil-pump drying. 1H-NMR (ppm, $CDCl_3$, 400 MHz): 1.59 – 1.85 (m, 5H), 2.18 – 2.35 (m, 3H), 2.54 (s, 3H, Me), 2.7 – 3.09 (3H), 6.94 – 7.58 (m, 10H), 8.18 (d, J = 1.1 Hz), 8.25 (d, J = 8.6 Hz, 1H), 8.81 (br. s., 1H, NH). $C_{31}H_{27}ClN_2O_4$ (526.0): HPLCMS: m/z = 526 [M], purity 97%.

6-{2-[2-(2,3-Dihydro-7-benzofuranyl)-2-methylpropyl]-2-hydroxy-3-octynoylamino}-4-methyl-2,3-benzoxazin-1-one 6



Reaction of 1-hexyne (0.4 ml), nBuLi (0.7 ml, 1.6 M in hexane) and 6-[4-(2,3-dihydro-7-benzofuranyl)-4-methyl-2-oxopentanoylamino]-4-methyl-2,3-benzoxazin-1-one (99.5 mg) at -78°C in THF (3 ml) as described for Example 1 gave, after column chromatography on silica gel and drying in vacuo, a solidified colourless oil (42 mg). 1H NMR (ppm, $CDCl_3$, 400 MHz): 0.89 (t, J =7.2 Hz, 3H, Me), 1.35 – 1.56 (m, 10H), 2.14 – 2.18 (m, 2H), 2.56 (s, 3H, Me), 2.66 (d, J =14.8 Hz, 1H), 2.73 (d, J = 14.8 Hz, 1H), 3.0 –3.2 (m, 2H), 3.27 (s, 1H), 4.57 (t, J = 9.3 Hz, 2H), 6.75 (t, J = 7.5 Hz, 1H), 6.95 (d, J = 6.3 Hz, 1H), 7.05 (d, J = 7.8 Hz, 1H), 7.50 – 7.52 (m, 1H), 8.23 – 8.29 (m, 2H), 8.78 (br. s., NH). $C_{29}H_{32}ClN_2O_5$ (488): LC-MS: m/z = 489 [M + H^+].

rac-6-{4-(2-Chloro-4-fluorophenyl)-2-hydroxy-2-[(4-hydroxyphenyl)ethynyl]-4-methylpentanoylamino}-4-methyl-2,3-benzoxazin-1-one 7

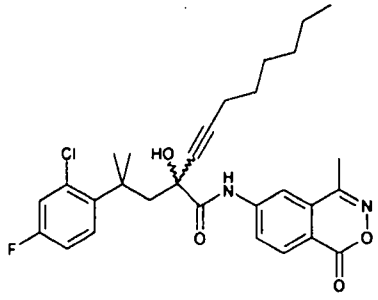


Stage A: a suspension of the compound of Example 10 (57.8 mg), triphenylphosphine (6.8 mg), copper iodide (5 mg), 4-iodophenyl acetate (51 mg), 5 mg of palladium acetate in THF (1 ml) and triethylamine (3 ml) was reacted in an ultrasonic bath under argon for 1 h. Addition of saturated aqueous ammonium chloride solution was followed by extraction with ethyl acetate and washing with water and brine. Drying with sodium sulphate was followed by concentration and purification by column chromatography on silica gel. A white solid (46.7 mg) was obtained. Stage B: A suspension of the compound from stage A (46.7 mg) and sodium bicarbonate (128 mg) in methanol was stirred at room temperature under argon for 6 h. A spatula tip of sodium bicarbonate was then added, and the mixture was stirred overnight. It was diluted with ethyl acetate,

water was added, and separation of the phases was followed by extraction with ethyl acetate. Washing of the combined organic phases with brine, drying over sodium sulphate, concentration and column chromatography on silica gel resulted in the title compound as a viscous oil (29 mg).

1H-NMR (ppm, $CDCl_3$, 400 MHz): 1.63 (s, 3H, Me), 1.69 (s, 3H, Me), 2.56 (s, 3H, Me), 2.94 – 3.01 (m, 3H), 5.48 (br. s, 1H, OH), 6.74 – 6.77 (m, 2H), 6.84 – 6.93 (m, 2H), 7.21 – 7.25 (m, 2H), 7.43 (dd, J = 9.0, 6.1 Hz, 1H), 7.57 – 7.59 (dd, J = 8.6, 2.3 Hz, 1H), 8.22 – 8.23 (m, 1H), 8.31 (d, J = 8.6 Hz, 1H), 8.80 (br. s, 1H, NH). $C_{29}H_{24}ClFN_2O_5$ (534.98): LC-MS: m/z = 535 [M + H^+].

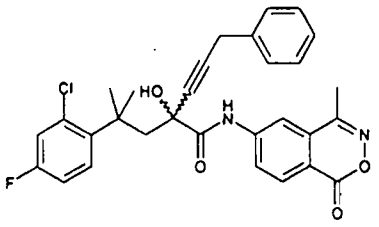
rac-6-{2-[2-(2-Chloro-4-fluorophenyl)-2-methylpropyl]-2-hydroxydec-3-ynoyl-amino}-4-methyl-2,3-benzoxazin-1-one 8



Reaction of 1-octyne (0.4 ml), nBuLi (0.6 ml, 1.6 M in hexane) and 6-[4-(2-chloro-4-fluorophenyl)-4-methyl-2-oxovaleroylamino]-4-methyl-2,3-benzoxazin-1-one (110 mg) in THF (3 ml) at -78°C as described for Example 1 gave, after column chromatography on silica gel, a white solid (25 mg).

1H-NMR (ppm, $CDCl_3$, 400 MHz): 0.87 (t, J = 7.0 Hz, 3H), 1.26 – 1.46 (m, 8H), 1.58 (s, 3H, Me), 1.63 (s, 3H, Me), 2.12 (t, J = 7.0 Hz, $CH_2C{\equiv}C$), 2.56 (s, 3H, Me)2.79 – 2.91 (m, 3H), 6.92 – 6.95 (m, 2H), 7.40 (dd, J = 8.9, 6.3 Hz, 1H), 7.53 (dd, J = 8.6, 1.9 Hz, 1H), 8.21 (d, J = 1.9 Hz, 1H), 8.30 (d, J = 8.6 Hz, 1H), 8.71 (br. s., 1H, NH); $C_{29}H_{32}ClFN_2O_4$ (527.0): LC-MS: m/z = 527 [M + H^+].

rac-6-{2-[2-(2-Chloro-4-fluorophenyl)-2-methylpropyl]-2-hydroxy-5-phenylpent-3-ynoylamino}-4-methyl-2,3-benzoxazin-1-one 9

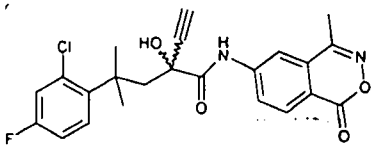


Reaction of 3-phenyl-1-propyne (0.17 ml), nBuLi (0.51 ml, 1.6 M in hexane) and 6-[4-(2-chloro-4-fluorophenyl)-4-methyl-2-oxovaleroylamino]-4-methyl-2,3-benzoxazin-1-one (140 mg) in THF (3 ml) at -78°C as described for Example 1 gave, after column chromatography on silica gel and drying in vacuo, a white foam (116 mg).

1H-NMR (ppm, $CDCl_3$, 400 MHz): 1.59 (s, 3H, Me), 1.61 (s, 3H, Me), 2.55 (s, 3H, Me), 2.79 – 2.95 (m, 3H), 3.4 – 3.6 (m, 2H, $CH_2C{\equiv}C$), 6.8 – 6.93 (m, 2H), 7.23 – 7.42 (m, 7H), 8.15 (d, J = 2.3 Hz, 1H), 8.27 (d, J = 8.6 Hz, 1H), 8.64 (br. s., 1H, NH).

$C_{30}H_{26}ClFN_2O_4$ (533.0): LC-MS: m/z = 533 [M + H^+].

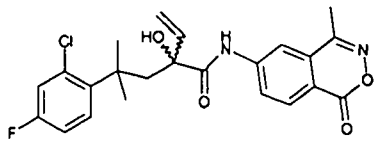
rac-6-{4-(2-Chloro-4-fluorophenyl)-2-ethynyl-2-hydroxy-4-methylpentanoylamino}-4-methyl-2,3-benzoxazin-1-one 10



Ethynylmagnesium bromide (2.2 ml, 0.5 M in THF) was added to an ice-cold solution of 6-[4-(2-chloro-4-fluorophenyl)-4-methyl-2-oxovaleroylamino]-4-methyl-2,3-benzoxazin-1-one (208 mg) in THF (4 ml). Under argon, the reaction solution was allowed to reach room temperature over the course of 3 h. Working up as described in Example 1 and column chromatography on silica gel resulted in the title compound as a foam (84 mg) after oil-pump drying. 1H-NMR (ppm, $CDCl_3$, 400 MHz): 0.8 – 0.9 (m, 1H), 1-58 (s, 3H, Me), 1.65 (s, 3H, Me), 2.56 – 2.96 (6H), 6.86 – 6.94 (m, 2H), 7.41 (dd, J = 9.0, 6.2 Hz, 1H), 7.56 (dd, J = 8.6, 1.9 Hz, 1H), 8.19 (d, J = 1.9 Hz, 1H), 8.31 (d, J = 8.6 Hz, 1H), 8.63 (br. s., 1H, NH).

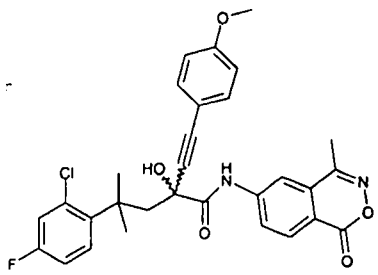
$C_{23}H_{20}ClFN_2O_4$ (542.9): LC-MS: m/z = 543 [M + H^+].

rac-6-{4-(2-Chloro-4-fluorophenyl)-2-hydroxy-4-methyl-2-vinyl-pentanoylamino}-4-methyl-2,3-benzoxazin-1-one 11



A vinylmagnesium bromide solution (0.5 ml, 1M in THF) was injected into 6-[4-(2-chloro-4-fluorophenyl)-4-methyl-2-oxovaleroylamino]-4-methyl-2,3-benzoxazin-1-one (103 mg) in THF (3 ml) at -78°C, and the mixture was allowed to reach room temp. under argon overnight. Addition of aqueous ammonium chloride solution was followed by extraction with ethyl acetate and washing with sat. sodium chloride solution. Drying with sodium sulphate was followed by concentration in a rotary evaporator and purification by column chromatography on silica gel to result in the title compound as solidified oil (18 mg). 1H-NMR (ppm, $CDCl_3$, 400 MHz, selected signals): 1.53 (s, 3H, Me), 1.57 (s, 3H, Me), 2.35 (s, 1H), 2.56 (s, 3H, Me), 2.74 (d, J = 15.3 Hz, 1H), 2.89 (d, J = 15.3 Hz, 1H), 5.15 (d, J = 10.5 Hz, 1H), 5.27 (d, J = 17.6 Hz, 1H), 6.10 (dd, J = 17.2, 10.6 Hz, 1H), 6.81 – 6.86 (m, 1H),

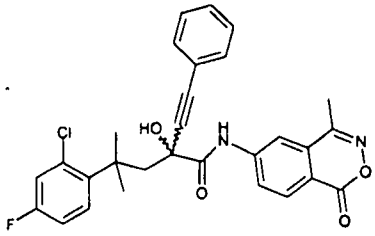
rac-6-{4-(2-Chloro-4-fluorophenyl)-2-hydroxy-2-[(4-methoxyphenyl)ethynyl]-4-methylpentanoylamino}-4-methyl-2,3-benzoxazin-1-one 12



Reaction of 4-methoxyphenylacetylene (0.4 ml), nBuLi (0.6 ml, 1.6 M in hexane) and 6-[4-(2-chloro-4-fluorophenyl)-4-methyl-2-oxovaleroylamino]-4-methyl-2,3-benzoxazin-1-one (110 mg) at -78°C as described for Example 1 gave, after column chromatography on silica gel, the title compound as a white solid (44 mg).
1H-NMR (ppm, $CDCl_3$, 400 MHz): 1.63 (s, 3H, Me), 1.69 (s, 3H, Me), 2.91 – 3.01 (m, 3H), 3.81 (s, 3H, Me), 6.81 – 6.94 (m, 3H), 7.25 – 7.29 (m, 3H), 7.43 (dd, J = 8.4, 6.3

Hz, 1H), 7.58 (dd, J = 8.6, 2.3 Hz, 1H), 8.24 (d, J = 1.9 Hz, 1H), 8.31 (d, J = 8.6 Hz, 1H), 8.79 (br. s., 1H, NH). $C_{30}H_{26}ClFN_2O_5$ (549.0): LC-MS: m/z = 549 [M + H$^+$].

rac-6-{4-(2-Chloro-4-fluorophenyl)-2-hydroxy-4-methyl-2-(phenylethynyl)-pentanoylamino}-4-methyl-2,3-benzoxazin-1-one 13

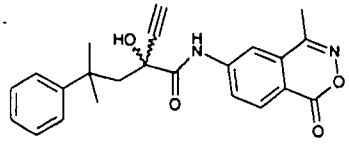


Lithium phenylacetylide (0.65 ml, 1M in THF) was added to 6-[4-(2-chloro-4-fluorophenyl)-4-methyl-2-oxovaleroylamino]-4-methyl-2,3-benzoxazin-1-one (136 mg) at -78°C and the mixture was stirred at -78°C under argon for 2.5 h. Working up as described for Example 1 and column chromatography on silica gel resulted in the title compound as a white foam (102 mg) after oil-pump drying.

1H-NMR (ppm, $CDCl_3$, 400 MHz): 1.64 (s, 3H, Me), 1.70 (s, 3H, Me), 2.57 (s, 3H, Me), 2.92 – 3.03 (m, 3H), 6.82 – 6.86 (m, 1H), 6.91 – 6.93 (m, 1H), 7.30 – 7.36 (m, 5H), 7.44 (dd, J = 9.0, 6.2 Hz, 1H), 7.59 (dd, J = 8.6, 2.0 Hz, 1H), 8.23 (d, J = 2.0 Hz, 1H), 8.31 (d, J = 8.2 Hz, 1H), 8.79 (br. s., NH); $C_{29}H_{24}ClFN_2O_4$ (519.0): HPLC-MS: m/z = 518 [M].

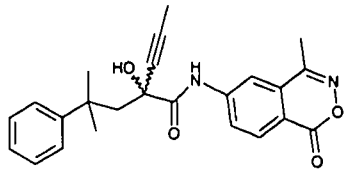
The compounds 14 and 15 were prepared in analogy to Example 10 from 6-(4-methyl-4-phenyl-2-oxovaleroylamino)-4-methyl-2,3-benzoxazin-1-one and the alkynyl-magnesium halide:

rac-6-[2-Ethynyl-2-hydroxy-4-methyl-4-phenylpentanoylamino]-4-methyl-2,3-benzoxazin-1-one 14



1H-NMR (ppm, $CDCl_3$, 400 MHz): 1.42 (3H), 1.59 (3H), 2.57 (3H), 2.64 (4H), 7.15 (1H), 7.31 (2H), 7.46 (2H), 7.58 (1H), 8.25 (1H), 8.30 (1H), 8.81 (1H).

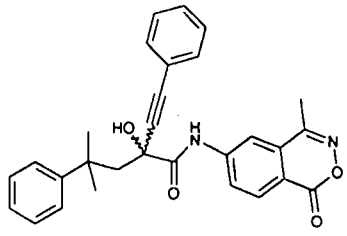
rac-6-[2-Hydroxy-4-methyl-4-phenyl-2-propynylpentanoylamino]-4-methyl-2,3-benzoxazin-1-one 15



1H-NMR (ppm, $CDCl_3$, 400 MHz): 1.42 (3H), 1.59 (3H), 2.50-2.65 (6H), 7.11 (1H), 7.30 (2H), 7.43 (2H), 7.58 (1H), 8.29 (2H), 8.85 (1H).

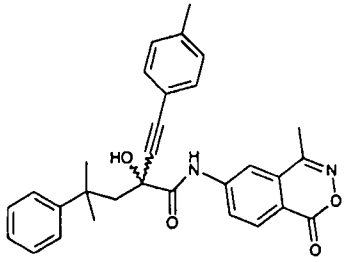
The compounds 15-28 were prepared in analogy to Example 1 from 6-(4-methyl-4-phenyl-2-oxovaleroylamino)-4-methyl-2,3-benzoxazin-1-one and the respective lithium arylacetylide:

rac-6-[2-Hydroxy-4-methyl-4-phenyl-2-(phenylethynyl)pentanoylamino]-4-methyl-2,3-benzoxazin-1-one 16



1H-NMR (ppm, $CDCl_3$, 300 MHz): 1.47 (3H), 1.65 (3H), 2.57 (3H), 2.62-2.78 (3H), 7.15 (1H), 7.27-7.37 (5H), 7.40 (2H), 7.50 (2H), 7.59 (1H), 8.29 (2H), 8.90 (1H).

(+)-6-[2-Hydroxy-4-methyl-2-[(4-methylphenyl)ethynyl]-4-phenylpentanoylamino]-4-methyl-2,3-benzoxazin-1-one 17a and
(-)-6-[2-Hydroxy-4-methyl-2-[(4-methylphenyl)ethynyl]-4-phenylpentanoylamino]-4-methyl-2,3-benzoxazin-1-one 17b

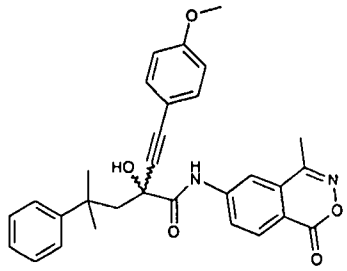


1H-NMR (ppm, $CDCl_3$, 300 MHz): 1.48 (3H), 1.64 (3H), 2.36 (3H), 2.57 (3H), 2.60-2.80 (3H), 7.08-7.20 (3H), 7.30 (4H), 7.49 (2H), 7.60 (1H), 8.29 (2H), 8.90 (1H).

16a: $[\alpha]^D_{20}$: +28.4° ($CHCl_3$, 1.03 g/100 ml; λ=589 nm)

16b: $[\alpha]^D_{20}$: -28.6° ($CHCl_3$, 1.01 g/100 ml; λ=589 nm)

rac-6-[2-Hydroxy-2-[(4-methoxyphenyl)ethynyl]-4-methyl-4-phenylpentanoyl-amino]-4-methyl-2,3-benzoxazin-1-one 18



1H-NMR (ppm, $CDCl_3$, 300 MHz): 1.47 (3H), 1.63 (3H), 2.56 (3H), 2.60-2.78 (3H), 3.80 (3H), 6.81 (2H), 7.13 (1H), 7.25-7.38 (4H), 7.48 (2H), 7.60 (1H), 8.28 (2H), 8.89 (1H).

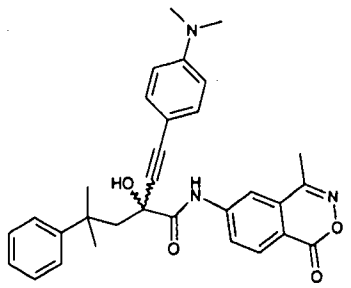
(+)-6-[2-Hydroxy-2-[(4-methoxyphenyl)ethynyl]-4-methyl-4-phenylpentanoylamino]-4-methyl-2,3-benzoxazin-1-one 18a and
(-)-6-[2-Hydroxy-2-[(4-methoxyphenyl)ethynyl]-4-methyl-4-phenylpentanoylamino]-4-methyl-2,3-benzoxazin-1-one 18b

The racemic mixture which was described in example **18** was separated by preparative chiral HPLC (column Chiralpak AD 250x10 mm) into the enantiomers **18a** and **18b**.

18a : $[\alpha]^D_{20}$: + 29.3° ($CHCl_3$, 1.12 g/100 ml; λ=589 nM)

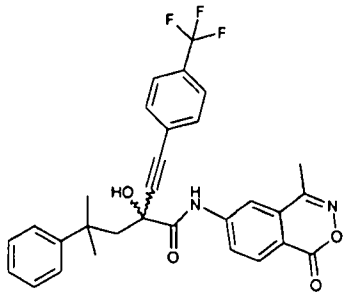
18b : $[\alpha]^D_{20}$: - 30.0° ($CHCl_3$, 1.14 g/100 ml; λ=589 nM)

rac-6-[2-Hydroxy-2-[(4-(N,N-dimethylamino)phenyl)ethynyl]-4-methyl-4-phenyl-pentanoylamino]-4-methyl-2,3-benzoxazin-1-one 19



1H-NMR (ppm, $CDCl_3$, 400 MHz): 1.48 (3H), 1.62 (3H), 2.57 (3H), 2.60-2.75 (3H), 2.98 (6H), 6.58 (2H), 7.12 (1H), 7.23-7.38 (4H), 7.48 (2H); 7.57 (1H), 8.28 (2H), 8.90 (1H).

rac-6-[2-Hydroxy-4-methyl-4-phenyl-2-[(4-trifluoromethylphenyl)ethynyl]-pentanoylamino]-4-methyl-2,3-benzoxazin-1-one 20



1H-NMR (ppm, $CDCl_3$, 400 MHz): 1.48 (3H), 1.63 (3H), 2.57 (3H), 2.64-2.80 (3H), 7.17 (1H), 7.33 (2H), 7.48 (4H), 7.56 (2H), 7.61 (1H), 8.30 (2H), 8.92 (1H).

(+)-6-[2-Hydroxy-4-methyl-4-phenyl-2-[(4-trifluormethylphenyl)ethynyl]-pentanoylamino]-4-methyl-2,3-benzoxazin-1-one 20a and

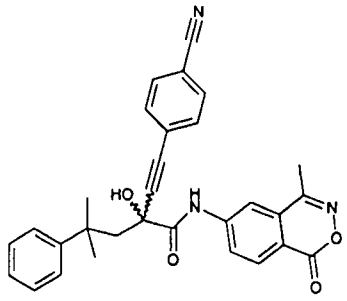
(-)-6-[2-Hydroxy-4-methyl-4-phenyl-2-[(4-trifluormethylphenyl)ethynyl]-pentanoylamino]-4-methyl-2,3-benzoxazin-1-one 20b

The racemic mixture which was described in example **20** was separated by preparative chiral HPLC (column Chiralpak AD 250x10 mm) into the enantiomers **20a** and **20b**.

20a : $[\alpha]^{D}_{20}$: + 19.9° ($CHCl_3$, 1.05 g/100 ml; λ=589 nM)

20b : $[\alpha]^{D}_{20}$: - 20.4° ($CHCl_3$, 1.01 g/100 ml; λ=589 nM)

rac-6-[2-[(4-Cyanophenyl)ethynyl]-2-hydroxy-4-methyl-4-phenylpentanoylamino]-4-methyl-2,3-benzoxazin-1-one 21



1H-NMR (ppm, $CDCl_3$, 400 MHz): 1.50 (3H), 1.62 (3H), 2.57 (3H), 2.63-2.82 (3H), 7.18 (1H), 7.35 (2H), 7.48 (4H), 7.55-7.68 (2H), 7.62 (1H), 8.30 (2H), 8.94 (1H).

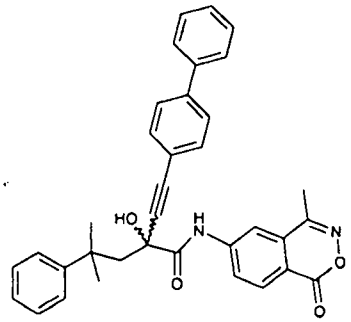
(+)-6-[2-[(4-Cyanophenyl)ethynyl]-2-hydroxy-4-methyl-4-phenylpentanoylamino]-4-methyl-2,3-benzoxazin-1-one 21a and
(-)-6-[2-[(4-Cyanophenyl)ethynyl]-2-hydroxy-4-methyl-4-phenylpentanoylamino]-4-methyl-2,3-benzoxazin-1-one 21b

The racemic mixture which was described in example **21** was separated by preparative chiral HPLC (column Chiralpak AD 250x10 mm) into the enantiomers **21a** and **21b**.

21a : $[\alpha]^{D}_{20}$: + 26.6° ($CHCl_3$, 1.12 g/100 ml; λ=589 nM)

21b : $[\alpha]^{D}_{20}$: - 26.8° ($CHCl_3$, 1.02 g/100 ml; λ=589 nM)

rac-6-[2-Hydroxy-4-methyl-4-phenyl-2-[(4-phenylphenyl)ethynyl]pentanoylamino]-4-methyl-2,3-benzoxazin-1-one 22



1H-NMR (ppm, $CDCl_3$, 400 MHz): 1.50 (3H), 1.68 (3H), 2.58 (3H), 2.64-2.81 (3H), 7.18

(1H), 7.30-7.40 (3H), 7.41-7.61 (11H), 8.30 (2H), 8.92 (1H).

(+)-6-[2-Hydroxy-4-methyl-4-phenyl-2-[(4-phenylphenyl)ethynyl]pentanoylamino]-4-methyl-2,3-benzoxazin-1-one 22a and

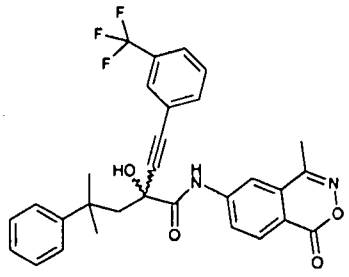
(-)-6-[2-Hydroxy-4-methyl-4-phenyl-2-[(4-phenylphenyl)ethynyl]pentanoylamino]-4-methyl-2,3-benzoxazin-1-one 22b

The racemic mixture which was described in example **22** was separated by preparative chiral HPLC (column Chiralpak AD 250x10 mm) into the enantiomers **22a** and **22b**.

22a : $[\alpha]^{D}_{20}$: + 38.4° ($CHCl_3$, 1.06 g/100 ml; λ=589 nM)

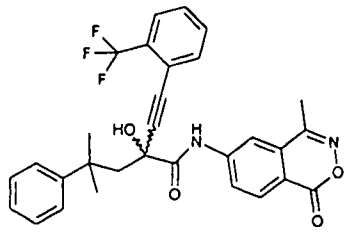
22b : $[\alpha]^{D}_{20}$: - 30.6° ($CHCl_3$, 1.12 g/100 ml; λ=589 nM)

rac-6-[2-Hydroxy-4-methyl-4-phenyl-2-[(3-trifluoromethylphenyl)ethynyl]-pentanoylamino]-4-methyl-2,3-benzoxazin-1-one 23



1H-NMR (ppm, $CDCl_3$, 300 MHz): 1.52 (3H), 1.68 (3H), 2.60 (3H), 2.65-2.88 (3H), 7.21 (1H), 7.49 (2H), 7.42-7.70 (7H), 8.34 (2H), 8.96 (1H).

rac-6-[2-Hydroxy-4-methyl-4-phenyl-2-[(2-trifluoromethylphenyl)ethynyl]-pentanoylamino]-4-methyl-2,3-benzoxazin-1-one 24



1H-NMR (ppm, $CDCl_3$, 600 MHz): 1.52 (3H), 1.65 (3H), 2.62 (3H), 2.69 (1H), 2.78 (1H),

2.91 (1H), 7.11 (1H), 7.32 (3H), 7.51 (3H), 7.57 (2H), 7.70 (1H), 8.20 (1H), 8.45 (1H), 8.75 (1H).

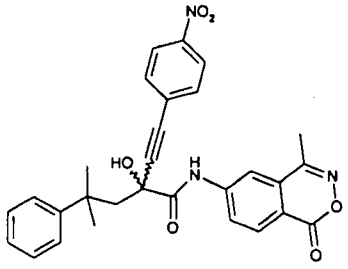
(+)-6-[2-Hydroxy-4-methyl-4-phenyl-2-[(2-trifluormethylphenyl)ethynyl]-pentanoylamino]-4-methyl-2,3-benzoxazin-1-one 24a and **(-)-6-[2-Hydroxy-4-methyl-4-phenyl-2-[(2-trifluormethylphenyl)ethynyl]-pentanoylamino]-4-methyl-2,3-benzoxazin-1-one 24b**

The racemic mixture which was described in example **24** was separated by preparative chiral HPLC (column Chiralpak AD 250x10 mm) into the enantiomers **24a** and **24b**.

24a : $[\alpha]^{D}_{20}$: + 21.3° ($CHCl_3$, 1.00 g/100 ml; λ=589 nM)

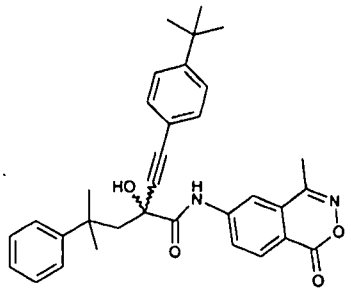
24b : $[\alpha]^{D}_{20}$: - 19.4° ($CHCl_3$, 1.00 g/100 ml; λ=589 nM)

rac-6-[2-Hydroxy-4-methyl-2-[(4-nitrophenyl)ethynyl]-4-phenylpentanoylamino]-4-methyl-2,3-benzoxazin-1-one 25



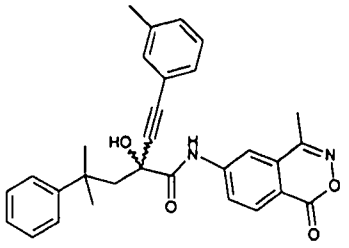
1H-NMR (ppm, $CDCl_3$, 600 MHz): 1.47 (3H), 1.62 (3H), 2.55 (3H), 2.79 (1H), 2.81 (2H), 7.18 (1H), 7.34 (2H), 7.50 (4H), 7.63 (1H), 8.17 (2H), 8.80 (2H), 8.94 (1H).

rac-6-[2-[[4-(1,1-Dimethylethyl)phenyl]ethynyl]-2-hydroxy-4-methyl-4-phenylpentanoylamino]-4-methyl-2,3-benzoxazin-1-one 26



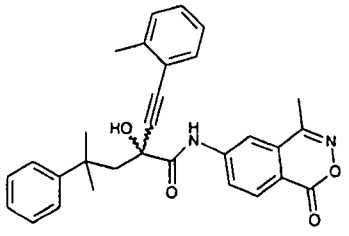
1H-NMR (ppm, $CDCl_3$, 300 MHz): 1.32 (9H), 1.51 (3H), 1.68 (3H), 2.62 (3H), 2.65-2.82 (3H), 7.18 (1H), 7.30-7.40 (6H), 7.52 (2H), 7.63 (1H), 8.32 (2H), 8.93 (1H).

rac-6-[2-Hydroxy-4-methyl-2-[(3-methylphenyl)ethynyl]-4-phenylpentanoylamino]-4-methyl-2,3-benzoxazin-1-one 27



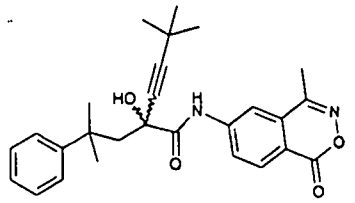
1H-NMR (ppm, $CDCl_3$, 400 MHz): 1.47 (3H), 1.63 (3H), 2.30 (3H), 2.58 (3H), 2.62-2.80 (3H), 7.12-7.26 (5H), 7.32 (2H), 7.50 (2H), 7.60 (1H), 8.30 (2H), 8.90 (1H).

rac-6-[2-Hydroxy-4-methyl-2-[(2-methylphenyl)ethynyl]-4-phenylpentanoylamino]-4-methyl-2,3-benzoxazin-1-one 28



1H-NMR (ppm, $CDCl_3$, 300 MHz): 1.47 (3H), 1.65 (3H), 2.38 (3H), 2.58 (3H), 2.62-2.80 (3H), 7.08-7.42 (7H), 7.49 (2H), 7.60 (1H), 8.22-8.36 (2H), 8.90 (1H).

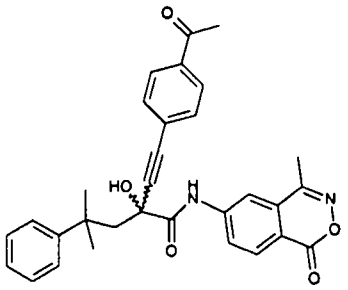
rac-6-[2-(3,3-Dimethylbutynyl)-2-hydroxy-4-methyl-4-phenylpentanoylamino]-4-methyl-2,3-benzoxazin-1-one 29



1H-NMR (ppm, $CDCl_3$, 300 MHz): 1.20 (9H), 1.43 (3H), 1.60 (3H), 2.46 (1H), 2.50-2.63 (5H), 7.11 (1H), 7.28 (2H), 7.43 (2H), 7.54 (1H), 8.22 (1H), 8.29 (1H), 8.32 (1H).

The following compound was prepared in analogy to Example 7 from the compound described in Example 13 and 4'-iodoacetophenone:

rac-6-[2-[(4-Acetylphenyl)ethynyl]-2-hydroxy-4-methyl-4-phenylpentanoylamino]-4-methyl-2,3-benzoxazin-1-one 30



1H-NMR (ppm, $CDCl_3$, 300 MHz): 1.48 (3H), 1.63 (3H), 2.56 (3H), 2.60 (3H), 2.63-2.82 (3H), 7.18 (1H), 7.33 (2H), 7.40-7.56 (4H), 7.62 (1H), 7.90 (2H), 8.30 (2H), 8.93 (1H).

(+)-6-[2-[(4-Acetylphenyl)ethynyl]-2-hydroxy-4-methyl-4-phenylpentanoylamino]-4-methyl-2,3-benzoxazin-1-one 30a and

(-)-6-[2-[(4-Acetylphenyl)ethynyl]-2-hydroxy-4-methyl-4-phenylpentanoylamino]-4-methyl-2,3-benzoxazin-1-one 30b

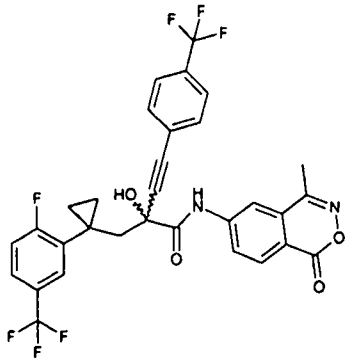
The racemic mixture which was described in example **30** was separated by preparative chiral HPLC (column Chiralpak AD 250x10 mm) into the enantiomers **30a** and **30b**.

30a : $[\alpha]^{D}_{20}$: + 31.3° ($CHCl_3$, 1.09 g/100 ml; λ=589 nM)

30b : $[\alpha]^{D}_{20}$: - 28.4° ($CHCl_3$, 1.09 g/100 ml; λ=589 nM)

The compounds 30 and 31 were prepared in analogy to Example 1 from 6-[3-[1-(2-fluoro-5-trifluoromethylphenyl)cyclopropyl]-2-oxopropionylamino]-4-methyl-2,3-benzoxazin-1-one

rac-6-[2-[(2-Fluoro-5-trifluoromethylphenyl)cyclopropylmethyl]-2-hydroxy-4-(4-trifluoromethylphenyl)but-3-inoylamino]-4-methyl-2,3-benzoxazin-1-one 31



1H-NMR (ppm, $CDCl_3$, 400 MHz): 0.90 (1H), 1.00-1.15 (3H), 2.51 (1H), 2.55 (3H), 2.68 (1H), 3.18 (1H), 7.01 (1H), 7.30 (1H), 7.41 (2H), 7.56 (2H), 7.63 (1H), 7.68 (1H), 8.19 (1H), 8.31 (1H), 8.98 (1H).

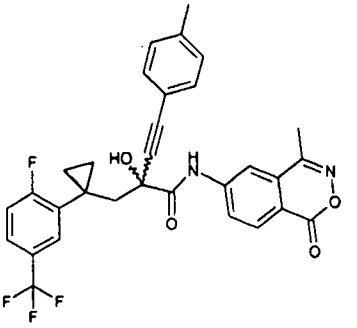
(+)-6-[2-[(2-Fluor-5-trifluormethylphenyl)cyclopropylmethyl]-2-hydroxy-4-(4-trifluormethylphenyl)but-3-inoylamino]-4-methyl-2,3-benzoxazin-1-one 31a and **(-)-6-[2-[(2-Fluor-5-trifluormethylphenyl)cyclopropylmethyl]-2-hydroxy-4-(4-trifluormethylphenyl)but-3-inoylamino]-4-methyl-2,3-benzoxazin-1-one 31b**

The racemic mixture which was described in example **31** was separated by preparative chiral HPLC (column Chiralpak AD 250x10 mm) into the enantiomers **31a** and **31b**.

31a : $[\alpha]^{D}_{20}$: + 2.3° ($CHCl_3$, 1.00 g/100 ml; λ=589 nM)

31b : $[\alpha]^{D}_{20}$: - 1.9° ($CHCl_3$, 1.00 g/100 ml; λ=589 nM)

rac-6-[2-[(2-Fluoro-5-trifluoromethylphenyl)cyclopropylmethyl]-2-hydroxy-4-(4-methylphenyl)but-3-ynoylamino]-4-methyl-2,3-benzoxazin-1-one 32



1H-NMR (ppm, $CDCl_3$, 400 MHz): 0.88 (1H), 0.98-1.13 (3H), 2.34 (3H), 2.44 (1H), 2.55 (3H), 2.70 (1H), 3.02 (1H), 7.01 (1H), 7.10 (2H), 7.22 (2H), 7.30 (1H), 7.64 (2H), 8.19 (1H), 8.31 (1H), 8.98 (1H).

(+)-6-[2-[(2-Fluor-5-trifluormethylphenyl)cyclopropylmethyl]-2-hydroxy-4-(4-methylphenyl)but-3-inoylamino]-4-methyl-2,3-benzoxazin-1-one 32a and **(-)-6-[2-[(2-Fluor-5-trifluormethylphenyl)cyclopropylmethyl]-2-hydroxy-4-(4-methylphenyl)but-3-inoylamino]-4-methyl-2,3-benzoxazin-1-one 32b**

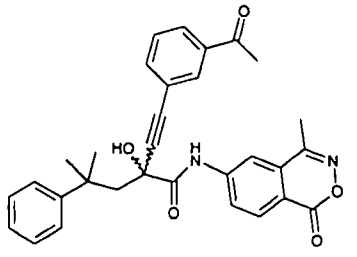
The racemic mixture which was described in example **32** was separated by preparative chiral HPLC (column Chiralpak AD 250x10 mm) into the enantiomers **32a** and **32b**.

32a : $[\alpha]^{D}_{20}$: + 8.6° ($CHCl_3$, 1.00 g/100 ml; λ=589 nM)

32b : $[\alpha]^{D}_{20}$: - 8.7° ($CHCl_3$, 1.00 g/100 ml; λ=589 nM)

The following compound was prepared in analogy to example 7 from compound which was described in example 14 and 3'-Iodacetophenon:

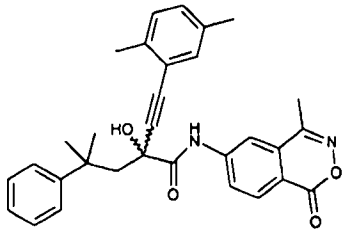
rac-6-[2-[(3-Acetylphenyl)ethynyl]-2-hydroxy-4-methyl-4-phenylpentanoylamino]-4-methyl-2,3-benzoxazin-1-one 33



1H-NMR (ppm, $CDCl_3$, 300 MHz): 1.49 (3H), 1.63 (3H), 2.57 (6H), 2.62-2.81 (3H), 7.16 81H), 7.28-7.70 (7H), 7.90-8.00 (2H), 8.30 (2H), 8.94 (1H).

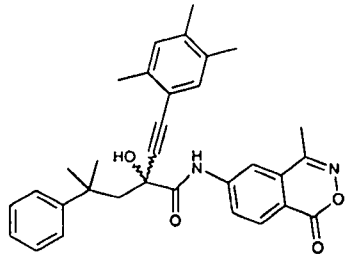
Compounds 34 and 35 were prepared in analogy to example 1 from 6-(4-Methyl-4-phenyl-2-oxovaleroylamino)-4-methyl-2,3-benzoxazin-1-one and the according Lithium arylacetylide.

rac-6-[2-[(2,5-Dimethylphenyl)ethynyl]-2-hydroxy-4-methyl-4-phenylpentanoylamino]-4-methyl-2,3-benzoxazin-1-one 34



1H-NMR (ppm, $CDCl_3$, 400 MHz): 1.49 (3H), 1.62 (3H), 2.27 (3H), 2.33 (3H), 2.57 (3H), 2.65-2.78 (3H), 7.03 (2H), 7.13 (2H), 7.30 (2H), 7.50 (2H), 7.61 (1H), 8.22 (1H), 8.30 (1H), 8.89 (1H).

rac-6-[2-[(2,4,5-Trimethylphenyl)ethynyl]-2-hydroxy-4-methyl-4-phenylpentanoylamino]-4-methyl-2,3-benzoxazin-1-one 35



1H-NMR (ppm, $CDCl_3$, 400 MHz): 1.47 (3H), 1.64 (3H), 2.18 (3H), 2.21 (3H), 2.30 (3H), 2.56 (3H), 2.65-2.77 (3H), 6.93 (1H), 7.12 (2H), 7.30 (2H), 7.48 (2H), 7.59 (1H), 8.22 (1H), 8.29 (1H), 8.90 (1H).

(+)-6-[2-[(2,4,5-Trimethylphenyl)ethynyl]-2-hydroxy-4-methyl-4-phenylpentanoylamino]-4-methyl-2,3-benzoxazin-1-one 35a and **(-)-6-[2-[(2,4,5-Trimethylphenyl)ethynyl]-2-hydroxy-4-methyl-4-phenylpentanoylamino]-4-methyl-2,3-benzoxazin-1-one 35b**

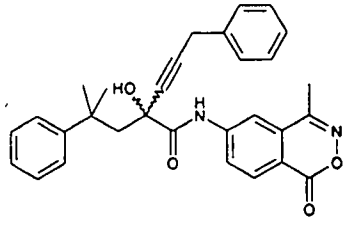
The racemic mixture which was described in example **35** was separated by preparative chiral HPLC (column Chiralpak AD 250x10 mm) into the enantiomers **35a** and **35b**.

35a : $[\alpha]^{D}_{20}$: + 30.6° ($CHCl_3$, 0.97 g/100 ml; λ=589 nM)

35b : $[\alpha]^{D}_{20}$: - 28.0° ($CHCl_3$, 0.96 g/100 ml; λ=589 nM)

The following compound was prepared in analogy to example 9 from 3-Phenyl-1-propine, nBuLi and 6-(4-Methyl-4-phenyl-2-oxovaleroylamino)-4-methyl-2,3-benzoxazin-1-one:

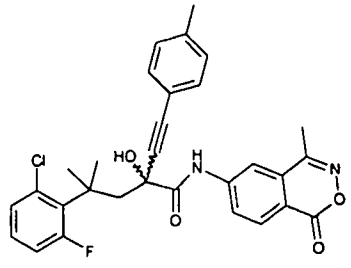
rac-6-{2-(2-phenyl)-2-methylpropyl]-2-hydroxy-5-phenylpent-3-inoylamino}-4-methyl-2,3-benzoxazin-1-one 36



1H-NMR (ppm, $CDCl_3$, 400 MHz): 1.42 (3H), 1.53 (3H), 2.55-2.70 (6H), 3.58 (2H), 7.11 (1H), 7.20-7.35 (7H), 7.41 (2H), 7.48 (1H), 8.20 (1H), 8.28 (1H), 8.80 (1H).

Compounds 37 and 38 were prepared in analogy to example 1 from 6-(4-Methyl-4-(2-chlor-6-fluorphenyl)-2-oxovaleroylamino)-4-methyl-2,3-benzoxazin-1-one and the according Lithium arylacetylide.

rac-6-[2-Hydroxy-4-methyl-4-(2-chlor-6-fluorphenyl)-2-(4-methylphenyl-ethinyl)pentanoylamino]-4-methyl-2,3-benzoxazin-1-one 37



1H-NMR (ppm, $CDCl_3$, 300 MHz): 1.73 (3H), 1.82 (3H), 2.33 (3H), 2.57 (3H), 2.88-3.02 (3H), 6.75-6.96 (2H), 7.01 (1H), 7.09 (2H), 7.27 (2H), 7.60 (1H), 8.22-8.35 (2H), 8.96 (1H).

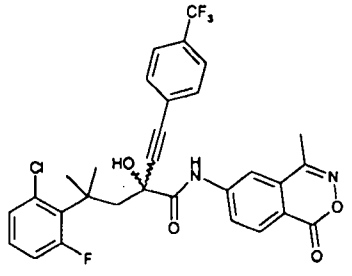
(+)-6-[2-Hydroxy-4-methyl-4-(2-chlor-6-fluorphenyl)-2-(4-methylphenyl-ethynyl)pentanoylamino]-4-methyl-2,3-benzoxazin-1-one 37a and **(-)-6-[2-Hydroxy-4-methyl-4-(2-chlor-6-fluorphenyl)-2-(4-methylphenyl-ethynyl)pentanoylamino]-4-methyl-2,3-benzoxazin-1-one 37b**

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

37a : $[\alpha]^{D}_{20}$: + 21.5° ($CHCl_3$, 1.00 g/100 ml; λ=589 nM)

37b : $[\alpha]^{D}_{20}$: - 21.0° ($CHCl_3$, 1.04 g/100 ml; λ=589 nM)

rac-6-[2-Hydroxy-4-methyl-4-(2-chlor-6-fluorphenyl)-2-(4-(trifluormethyl)phenyl-ethynyl)pentanoylamino]-4-methyl-2,3-benzoxazin-1-one 38



1H-NMR (ppm, $CDCl_3$, 400 MHz): 1.60 (3H), 1.93 (3H), 2.36 (1H), 2.56-2.72 (5H), 7.04 (1H), 7.14 (2H), 7.45 (2H), 7.53 (2H), 7.80 (1H), 8.35-8.45 (2H), 8.90 (1H).

(+)-6-[2-Hydroxy-4-methyl-4-(2-chlor-6-fluorphenyl)-2-(4-(trifluormethyl)phenyl-ethynyl)pentanoylamino]-4-methyl-2,3-benzoxazin-1-one 38a and **(-)-6-[2-Hydroxy-4-methyl-4-(2-chlor-6-fluorphenyl)-2-(4-(trifluormethyl)phenyl-ethynyl)pentanoylamino]-4-methyl-2,3-benzoxazin-1-one 38b**

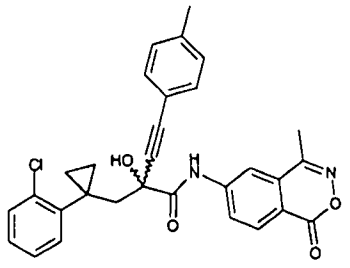
The racemic mixture which was described in example **38** was separated by preparative chiral HPLC (column Chiralpak AD 250x10 mm) into the enantiomers **38a** and **38b**.

38a : $[\alpha]^{D}_{20}$: + 143.2° ($CHCl_3$, 1.05 g/100 ml; λ=589 nM)

38b : $[\alpha]^{D}_{20}$: - 137.8° ($CHCl_3$, 1.12 g/100 ml; λ=589 nM)

Compounds 39 and 40 were prepared in analogy to example 1 from 6-(4-Methyl-4-(2-chlorphenyl)-2-oxovaleroylamino)-4-methyl-2,3-benzoxazin-1-one and the according Lithium arylacetylide.

rac-6-[2-(2-Chlorphenyl)cyclopropylmethyl]-2-hydroxy-4-(4-methylphenyl)but-3-inoylamino]-4-methyl-2,3-benzoxazin-1-one 39



1H-NMR (ppm, $CDCl_3$, 400 MHz): 0.84 (1H), 1.00 (1H), 1.08-1.22 (2H), 2.36 (3H), 2.53 (3H), 2.90 (1H), 7.03-7.18 (4H), 7.23-7.38 (3H), 7.50 (1H), 7.60 (1H), 8.22 (1H), 8.29 (1H), 8.91 (1H).

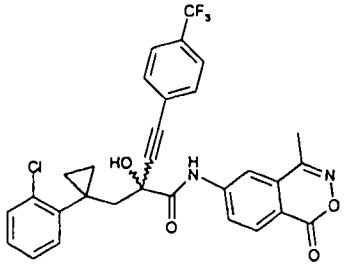
(+)-6-[2-(2-Chlorphenyl)cyclopropylmethyl]-2-hydroxy-4-(4-methylphenyl)but-3-inoylamino]-4-methyl-2,3-benzoxazin-1-one 39a and
(-)-6-[2-(2-Chlorphenyl)cyclopropylmethyl]-2-hydroxy-4-(4-methylphenyl)but-3-inoylamino]-4-methyl-2,3-benzoxazin-1-one 39b

The racemic mixture which was described in example **39** was separated by preparative chiral HPLC (column Chiralpak AD 250x10 mm) into the enantiomers **39a** and **39b**.

39a : $[\alpha]^{D}_{20}$: + 30.8° ($CHCl_3$, 1.00 g/100 ml; λ=589 nM)

39b : $[\alpha]^{D}_{20}$: - 28.3° ($CHCl_3$, 1.00 g/100 ml; λ=589 nM)

rac-6-[2-(2-Chlorphenyl)cyclopropylmethyl]-2-hydroxy-4-(4-trifluor-methylphenyl)but-3-inoylamino]-4-methyl-2,3-benzoxazin-1-one 40



1H-NMR (ppm, $CDCl_3$, 300 MHz): 0.91 (1H), 1.02 (1H), 1.08-1.25 (2H), 2.53 (3H), 3.00 (1H), 7.02-7.18 (2H), 7.28 (1H), 7.42-7.54 (3H), 7.55-7.67 (3H), 8.22 (1H), 8.32 (1H), 8.91 (1H).

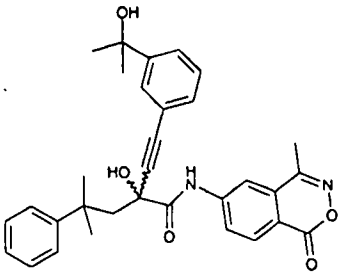
(+)-6-[2-(2-Chlorphenyl)cyclopropylmethyl]-2-hydroxy-4-(4-trifluor-methylphenyl)but-3-inoylamino]-4-methyl-2,3-benzoxazin-1-one 40a and **(-)-6-[2-(2-Chlorphenyl)cyclopropylmethyl]-2-hydroxy-4-(4-trifluor-methylphenyl)but-3-inoylamino]-4-methyl-2,3-benzoxazin-1-one 40b**

The racemic mixture which was described in example **40** was separated by preparative chiral HPLC (column Chiralpak AD 250x10 mm) into the enantiomers **40a** and **40b**.

40a : $[\alpha]^{D}_{20}$: + 20.9° ($CHCl_3$, 1.06 g/100 ml; λ=589 nM)

40b : $[\alpha]^{D}_{20}$: - 20.6° ($CHCl_3$, 1.05 g/100 ml; λ=589 nM)

rac-6-[2-[[3-(1-Hydroxy-1-methylethyl)phenyl]ethynyl]-2-hydroxy-4-methyl-4-phenylpentanoylamino]-4-methyl-2,3-benzoxazin-1-one 41

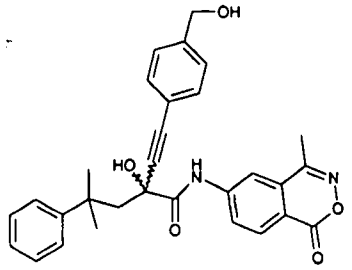


59 µl of 3 molar solution of Methylmagnesium chloride was diluted with 1 ml of pure Tetrahydrofurane. The solution was cooled to -70°C and a solution of 30 mg of the compound which was described in example 33 in 0,5 ml of pure Tetrahydrofurane was added. After stirring for 2,5 hours at -70°C the mixture was given to a saturated solution of ammonium chloride. After extracting the mixture with Ethyl acetate the combined organic phases were washed with saturated sodium chloride and dried over sodium sulphate. After column chromatography 16 mg of the product was obtained.

^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 1.46 (3H), 1.53 (6H), 1.62 (3H), 1.80 (1H), 2.55 (3H), 2.65-2.90 (3H), 7.12 (1H), 7.30 (3H), 7.40-7.52 (3H), 7.53 (1H), 7.60 (1H), 8.27 (2H), 8.95 (1H).

The following compound was prepared in analogy to example 7 from the compound which was described in example 14 and 4-Iodobenzylalcohol:

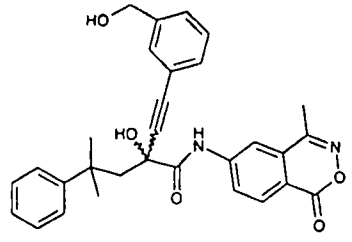
rac-6-[2-[[4-(Hydroxymethyl)phenyl]ethynyl]-2-hydroxy-4-methyl-4-phenylpentanoylamino]-4-methyl-2,3-benzoxazin-1-one 42



1H-NMR (ppm, $CDCl_3$, 300 MHz): 1.47 (3H), 1.60 (3H), 1.80 (1H), 2.57 (3H), 2.62-2.83 (3H), 4.68 (2H), 7.13 (1H), 7.25-7.43 (6H), 7.48 (2H), 7.59 (1H), 8.25-8.32 (2H), 8.91 (1H).

The following compound was prepared in analogy to example 7 from the compound which was described in example 14 and 4-Iodobenzylalcohol:

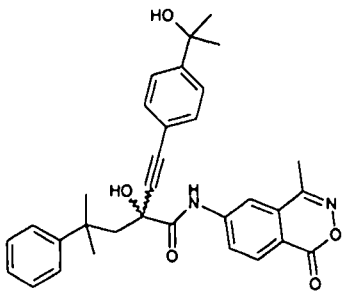
rac-6-[2-[[3-(Hydroxymethyl)phenyl]ethinyl]-2-hydroxy-4-methyl-4-phenylpentanoylamino]-4-methyl-2,3-benzoxazin-1-one 43



1H-NMR (ppm, $CDCl_3$, 400 MHz): 1.48 (3H), 1.62 (3H), 1.79 (1H), 2.57 (3H), 2.62-2.80 (3H), 4.68 (2H), 7.15 (1H), 7.25-7.39 (5H), 7.40 (1H), 7.49 (2H), 7.60 (1H), 8.29 (2H), 8.91 (1H).

The following compound was prepared in analogy to example 41 from the compound which was described in example 30 and a solution of Methyl magnesium chloride:

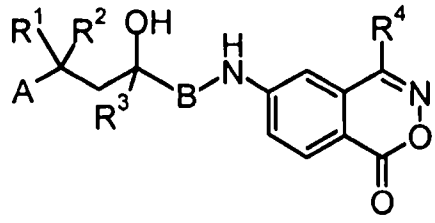
rac-6-[2-[[4-(1-Hydroxy-1-methylethyl)phenyl]ethynyl]-2-hydroxy-4-methyl-4-phenylpentanoylamino]-4-methyl-2,3-benzoxazin-1-one 44



1H-NMR (ppm, $CDCl_3$, 400 MHz): 1.47 (3H), 1.55 (6H), 1.62 (3H), 1.70 (1H), 2.55 (3H), 2.60-2.80 (3H), 7.14 (1H), 7.28-7.40 (4H), 7.41 (2H), 7.48 (2H), 7.60 (1H), 8.25-8.32 (2H), 8.90 (1H).

Claims

1. Compounds of the general formula I



(I),

R^1 and R^2 are independently of one another a hydrogen atom, a linear or nonlinear, branched or unbranched C_1-C_5-alkyl group, further forming together with the C atom of the chain a ring having a total of 3-7 members,

R^3 is a radical C≡C-R^a, where

R^a is a hydrogen or a C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_3-C_{10}-cycloalkyl, heterocycloalkyl optionally substituted one or more times, identically or differently, by K, or an aryl or heteroaryl optionally substituted one or more times, identically or differently by 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, -C=NOR^b -NR^cR^d or C_3-C_{10}-cycloalkyl, heterocycloalkyl optionally substituted one or more times, identically or differently, by M, or aryl or heteroaryl optionally substituted one or more times by L,

L is C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, 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 $-(CH_2)_{n+2}-$, where n is 1 or 2, and the terminal oxygen atoms and/or carbon atoms are linked to directly adjacent ring carbon atoms,

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

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

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

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

R^e is a hydrogen, C_1-C_6-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, 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, where

R^g and R^h are independently of one another a hydrogen or a C_1-C_8-alkyl, C_2-C_8-alkenyl or C_2-C_8-alkynyl optionally substituted one or more times, identically or differently, by 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 mentioned before for R^b, R^c and R^d, and

R^4 is a hydrogen atom, a methyl or an ethyl group or a partly or completely fluorinated C_1-C_3-alkyl group,

A is a mono- or bicyclic carbocyclic or heterocyclic aromatic ring which may optionally be substituted one or more times by C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_6-perfluoroalkyl, C_1-C_6-perfluoroalkoxy, C_1-C_8-alkoxy-C_1-C_8-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 -$(CH_2)_{n+2}$-, where n is 1 or 2, and the terminal oxygen atoms and/or carbon atoms are linked to directly adjacent ring carbon atoms, or

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

or

A is an alkenyl group -CR^5=CR^6R^7, where

R^5, R^6 and R^7 are identical or different and are independently of one another hydrogen atoms, halogen atoms, aryl

radicals or an unsubstituted or partly or completely fluorinated C_1-C_5–alkyl group, or

A is an alkynyl group -C≡CR^5, with the meaning stated above for R^5, and

B is a carbonyl or a CH_2 group

and their pharmaceutically acceptable salts.

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

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

4. Compounds according to Claim 1 to 3, in which R^3 is preferably alkenyl, alkynyl, arylalkynyl, heteroarylalkynyl, cycloalkylalkynyl, heterocycloalkylalkynyl.

5. Compounds according to any of the preceding claims, in which R^3 is preferably a vinyl, ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, hydroxypropynyl, hydroxybutynyl, 3-hydroxy-3-methylbutynyl, hydroxypentynyl, carboxypropynyl, t-butylcarboxypropynyl, phenylethynyl, (hydroxyphenyl)ethynyl, (methoxyphenyl)ethynyl, (dimethylaminophenyl)ethynyl, (methylphenyl)ethynyl, (cyanophenyl)ethynyl, (trifluoromethyl)ethynyl, (diphenyl)ethynyl, (nitrophenyl)ethynyl, (tert-butylphenyl)ethynyl, (acetylphenyl)ethynyl, (acetoxyphenyl)ethynyl, (carboxyphenyl)ethynyl or a benzylethynyl group.

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

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

8. Compounds according to Claim 7, in which A is preferably an unsubstituted or optionally mono- or polysubstituted phenyl radical.

9. Compounds according to Claim 8, where the phenyl radical is preferably substituted

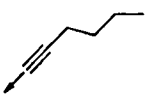
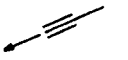
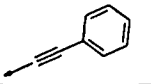
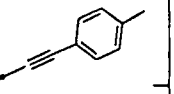
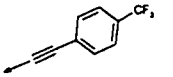
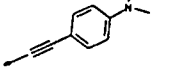
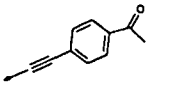
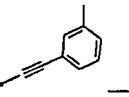
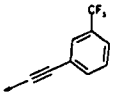
by one or two halogen atoms or one trifluoromethyl group.

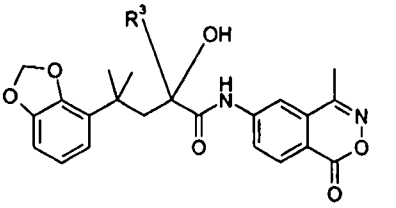
10. Compounds according to Claim 9, in which the halogen atoms are preferably chlorine and/or fluorine.

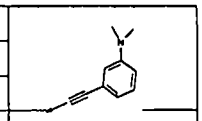
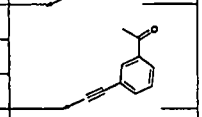
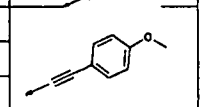
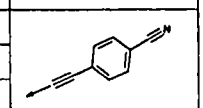
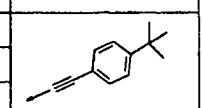
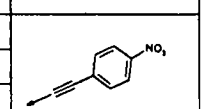
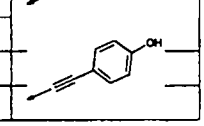
11. Compounds according to Claims 1-8, in which A is preferably a phenyl ring substituted by $-O-(CH_2)_n-O-$ or $-O-(CH_2)_n-CH_2-$, where the respectively directly adjacent ring carbon atoms are linked.

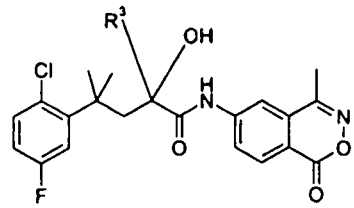
12. Compounds according to any of the preceding claims, in which R^4 is a hydrogen atom, a methyl or a trifluoromethyl radical.

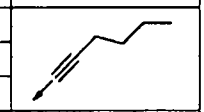
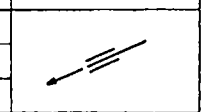
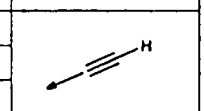
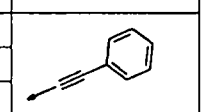
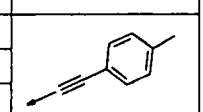
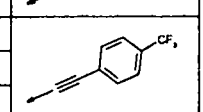
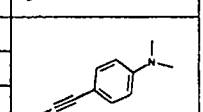
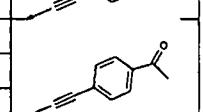
13. Compounds according to Claim 1 to 5, namely

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	-	



No.	Racemic or enantiomer	R3
52	rac	
53	-	
54	+	
55	rac	
56	+	
57	-	
58	rac	
59	+	
60	-	
61	rac	
62	+	
63	-	
64	rac	
65	+	
66	-	
67	rac	
68	+	
69	-	
70	rac	
71	+	
72	-	
73	rac	
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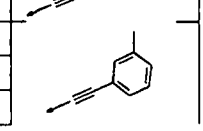
75	-	
76	rac	
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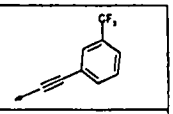
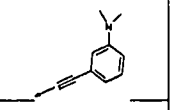
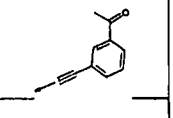
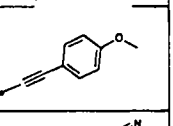
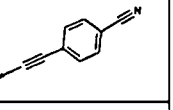
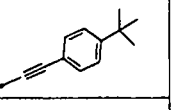
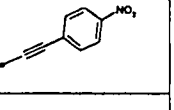
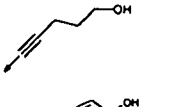
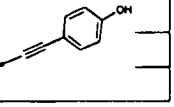
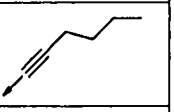
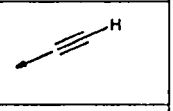
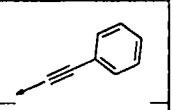
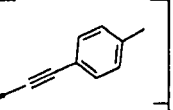
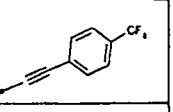
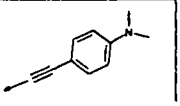
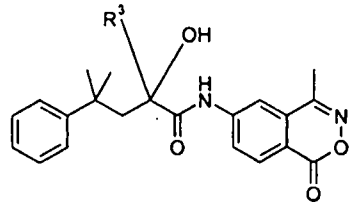
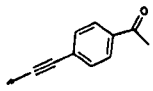
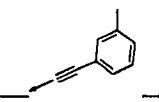
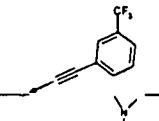
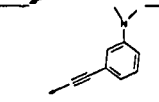
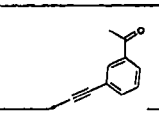
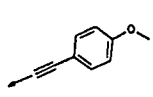
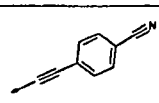
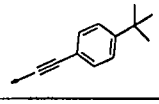
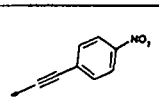
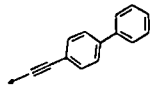
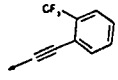
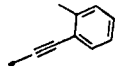
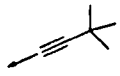
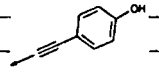
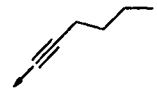
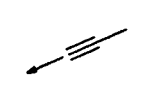
78	-	

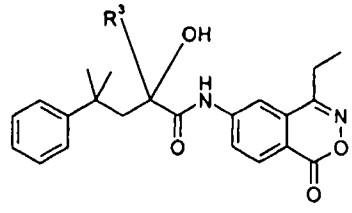
79	rac	
80	+	
81	-	
82	rac	
83	+	
84	-	
85	rac	
86	+	
87	-	
88	rac	
89	+	
90	-	
91	rac	
92	+	
93	-	
94	rac	
95	+	
96	-	
97	rac	
98	+	
99	-	
100	rac	
191	+	
102	-	
103	rac	
104	+	
105	-	

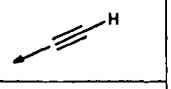
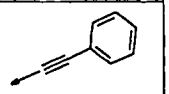
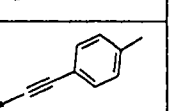
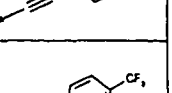
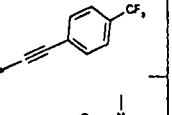
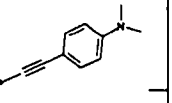
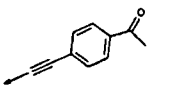
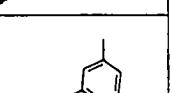
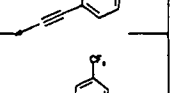
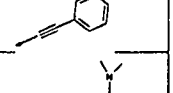
No.	Racemic or enantiomer	R3
106	rac	
107	-	
108	+	
109	rac	
110	+	
111	-	
112	rac	
113	+	
114	-	
115	rac	
116	+	
117	-	
118	rac	
119	+	
120	-	
121	rac	
122	+	
123	-	
124	rac	
125	+	
126	-	



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	-	

No.	Racemic or enantiomer	R3
169	rac	
170	-	
171	+	
172	rac	
173	+	
174	-	



175	rac	
176	+	
177	-	
178	rac	
179	+	
180	-	
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	
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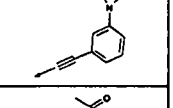
205	rac	
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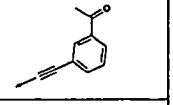
207	-	
208	rac	
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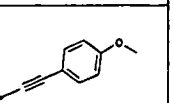
211	rac	
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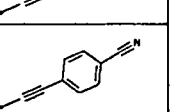
214	rac	
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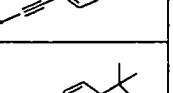
217	rac	
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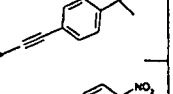
220	rac	
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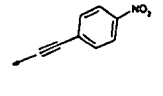
223	rac	
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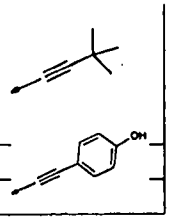
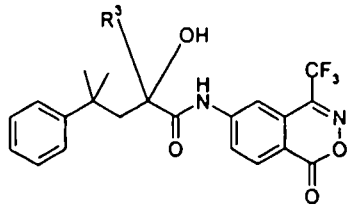
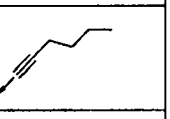
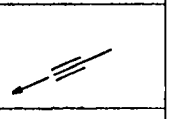
225	-	

226	rac	
227	+	
228	-	
229	rac	
230	+	
231	-	



No.	Racemic or enantiomer	R3
232	rac	
233	-	
234	+	
235	rac	
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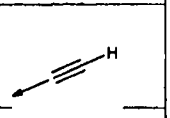
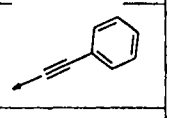
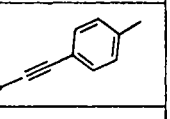
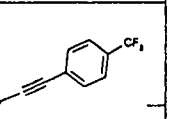
237	-	
238	rac	
239	+	
240	-	
241	rac	
242	+	
243	-	
244	rac	
245	+	
246	-	
247	rac	
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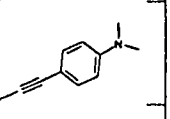
249	-	
250	rac	
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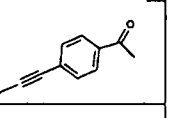
252	-	
253	rac	
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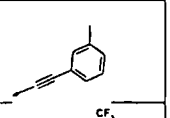
255	-	
256	rac	
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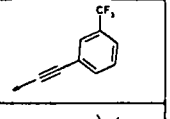
258	-	
259	rac	
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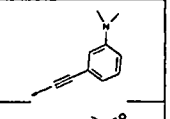
262	rac	
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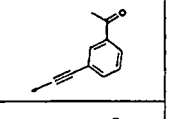
265	rac	
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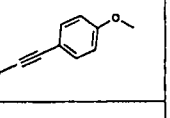
267	-	
268	rac	
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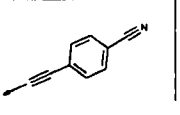
270	-	
271	rac	
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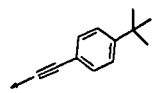
273	-	

274	rac	
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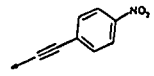
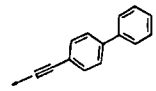
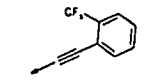
276	-	
277	rac	
278	+	
279	-	
280	rac	
281	+	
282	-	
283	rac	
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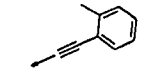
285	-	
286	rac	
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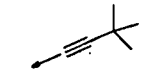
288	-	
289	rac	
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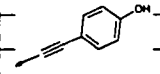
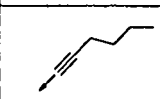
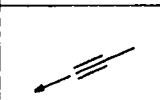
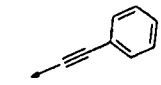
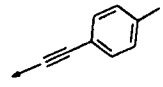
291	-	
292	rac	
293	+	
294	-	

No.	Racemic or enantiomer	R3
295	rac	
296	-	
297	+	
298	rac	
299	+	
300	-	
301	rac	
302	+	
303	-	
304	rac	
305	+	
306	-	
307	rac	
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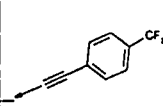
309	-	
310	rac	
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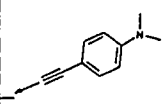
313	rac	
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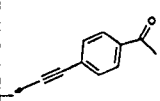
316	rac	
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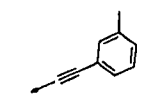
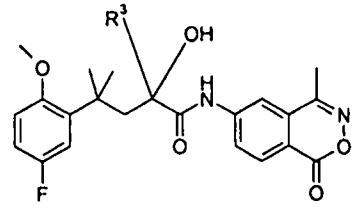
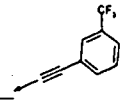
319	rac	
320	+	
321	-	



322	rac	
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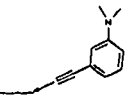
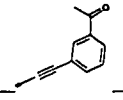
324	-	
325	rac	
326	+	
327	-	
328	rac	
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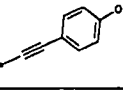
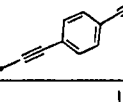
330	-	
331	rac	
332	+	
333	-	
334	rac	
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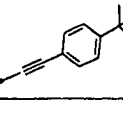
336	-	
337	rac	
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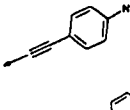
339	-	
340	rac	
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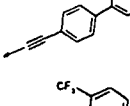
342	-	
343	rac	
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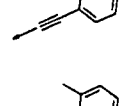
346	rac	
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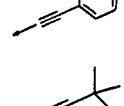
348	-	
349	rac	
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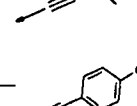
352	rac	
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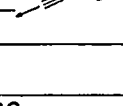
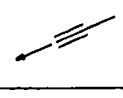
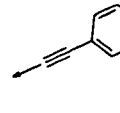
354	-	
355	rac	
356	+	
357	-	

No.	Racemic or enantiomer	R3
358	rac	
359	-	
360	+	
361	rac	
362	+	
363	-	
364	rac	
365	+	
366	-	
367	rac	
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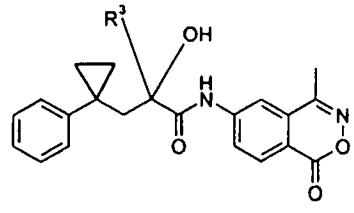
369	-	



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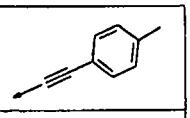
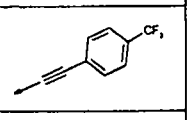
370	rac	
371	+	
372	-	
373	rac	
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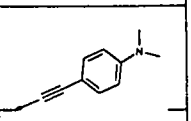
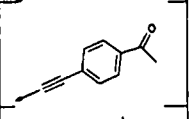
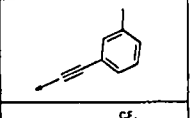
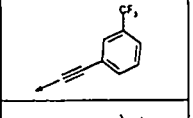
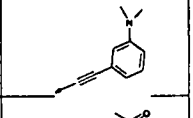
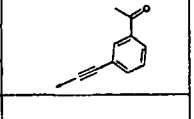
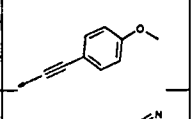
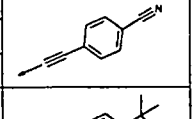
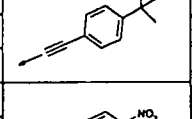
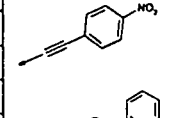
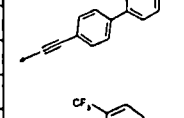
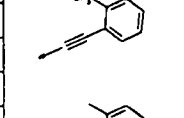
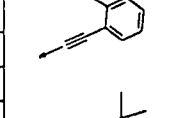
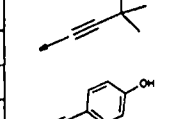
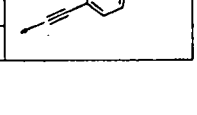
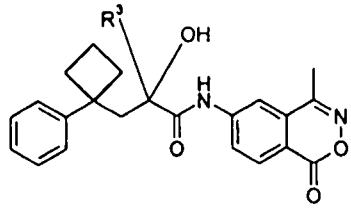
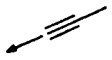
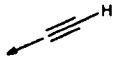
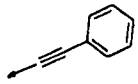
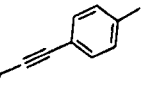
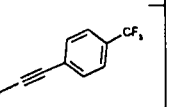
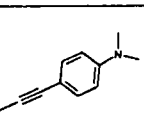
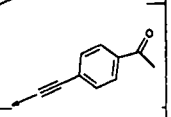
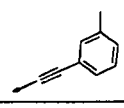
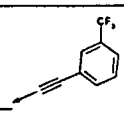
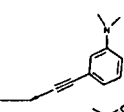
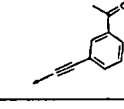
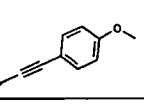
375	-	
376	rac	
377	+	
378	-	
379	rac	
380	+	
381	-	
382	rac	
383	+	
384	-	
385	rac	
386	+	
387	-	
388	rac	
389	+	
390	-	
391	rac	
392	+	
393	-	
394	rac	
395	+	
396	-	
397	rac	
398	+	
399	-	
400	rac	
401	+	
402	-	
403	rac	
404	+	
405	-	
406	rac	
407	+	
408	-	
409	rac	
410	+	
411	-	
412	rac	
413	+	
414	-	
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	
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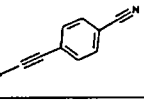
459	-	
460	rac	
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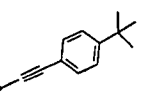
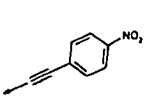
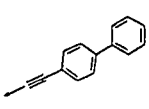
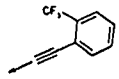
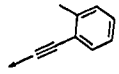
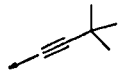
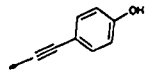
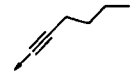
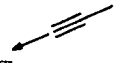
462	-	
463	rac	
464	+	
465	-	
466	rac	
467	+	
468	-	
469	rac	
470	+	
471	-	

472	rac	
473	+	
474	-	
475	rac	
476	+	
477	-	
478	rac	
479	+	
480	-	
481	rac	
482	+	
483	-	

No.	Racemic or enantiomer	R3
484	rac	
485	-	
486	+	
487	rac	
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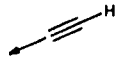
490	rac	
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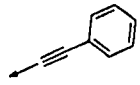
493	rac	
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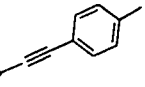
496	rac	
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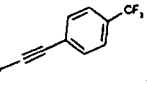
499	rac	
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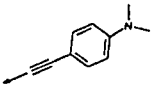
502	rac	
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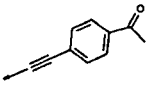
505	rac	
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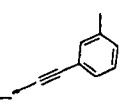
508	rac	
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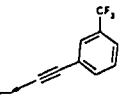
511	rac	
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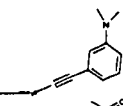
514	rac	
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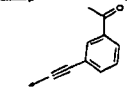
517	rac	
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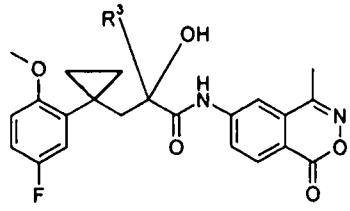
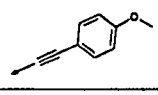


520	rac	
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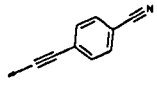
523	rac	
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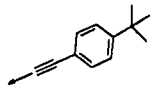
525	-	
526	rac	
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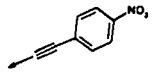
529	rac	
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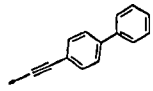
532	rac	
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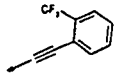
535	rac	
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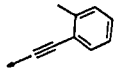
538	rac	
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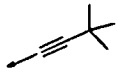
541	rac	
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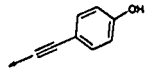
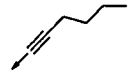
544	rac	
545	+	
546	-	

No.	Racemic or enantiomer	R3
547	rac	
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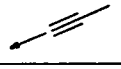
549	+	
550	rac	
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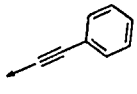
552	-	
553	rac	
554	+	
555	-	
556	rac	
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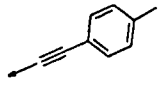
559	rac	
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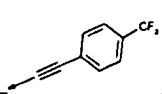
562	rac	
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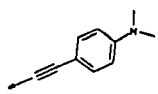
564	-	
565	rac	
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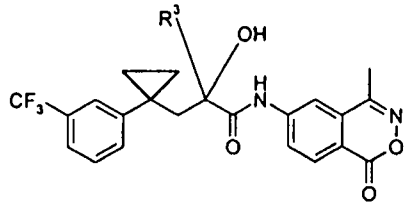
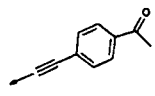
567	-	



568	rac	
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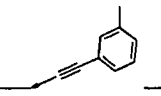
571	rac	
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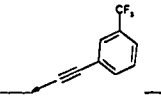
573	-	
574	rac	
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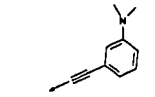
576	-	
577	rac	
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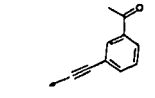
580	rac	
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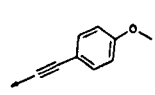
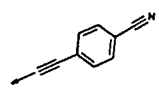
583	rac	
584	+	
585	-	
586	rac	
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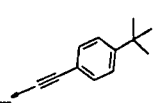
588	-	
589	rac	
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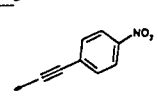
592	rac	
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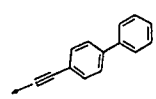
595	rac	
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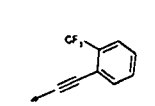
597	-	
598	rac	
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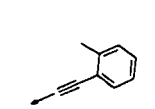
601	rac	
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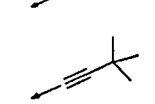
603	-	
604	rac	
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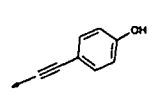
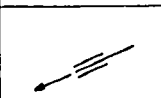
607	rac	
608	+	
609	-	

No.	Racemic or enantiomer	R3
610	rac	
611	-	
612	+	
613	rac	
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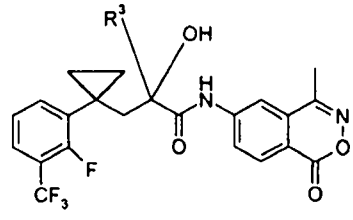
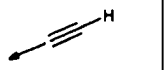
615	-	



616	rac	
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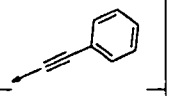
618	-	
619	rac	
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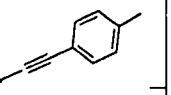
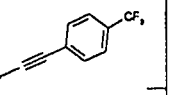
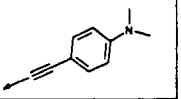
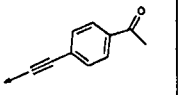
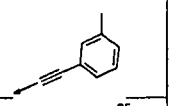
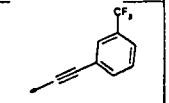
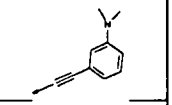
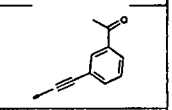
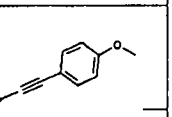
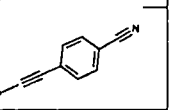
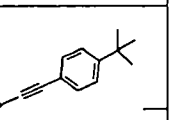
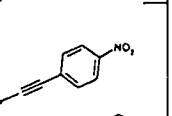
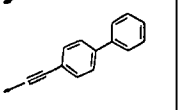
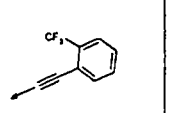
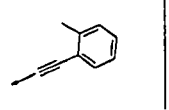
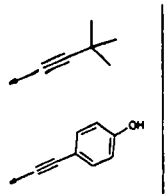
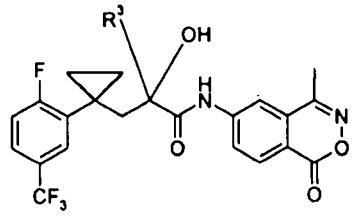
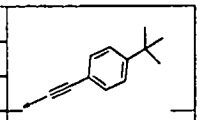
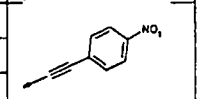
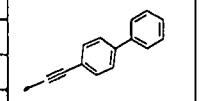
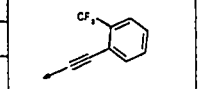
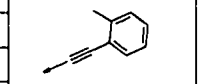
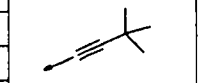
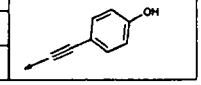
621	-	
622	rac	
623	+	
624	-	
625	rac	
626	+	
627	-	
628	rac	
629	+	
630	-	
631	rac	
632	+	
633	-	
634	rac	
635	+	
636	-	
637	rac	
638	+	
639	-	
640	rac	
641	+	
642	-	
643	rac	
644	+	
645	-	
646	rac	
647	+	
648	-	
649	rac	
650	+	
651	-	
652	rac	
653	+	
654	-	
655	rac	
656	+	
657	-	
658	rac	
659	+	
660	-	
661	rac	
662	+	
663	-	
664	rac	
665	+	
666	-	

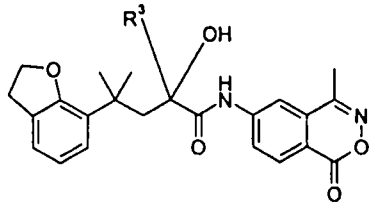
667	rac
668	+
669	-
670	rac
671	+
672	-

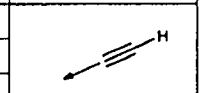
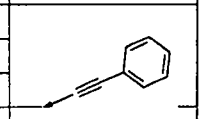
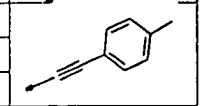
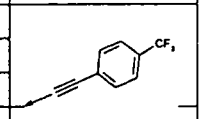
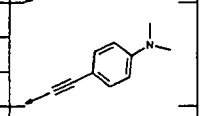
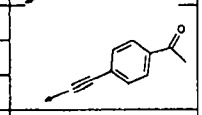
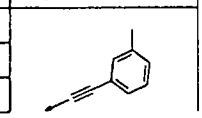


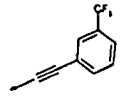
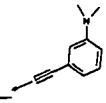
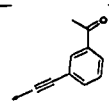
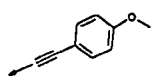
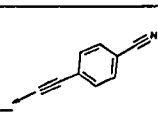
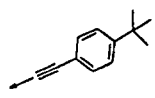
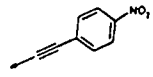
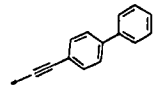
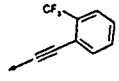
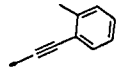
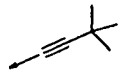
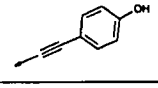
No.	Racemic or enantiomer	R3
673	rac	
674	-	
675	+	
676	rac	
677	+	
678	-	
679	rac	
680	+	
681	-	
682	rac	
683	+	
684	-	
685	rac	
686	+	
687	-	
688	rac	
689	+	
690	-	
691	rac	
692	+	
693	-	
694	rac	
695	+	
696	-	
697	rac	
698	+	
699	-	
700	rac	
701	+	
702	-	
703	rac	
704	+	
705	-	
706	rac	
707	+	
708	-	
709	rac	
710	+	
711	-	
712	rac	
713	+	
714	-	

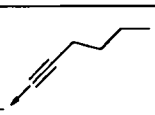
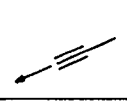
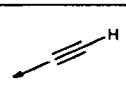
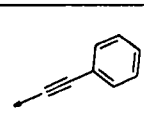


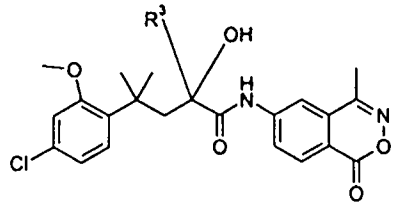
715	rac	
716	+	
717	-	
718	rac	
719	+	
720	-	
721	rac	
722	+	
723	-	
724	rac	
725	+	
726	-	
727	rac	
728	+	
729	-	
730	rac	
731	+	
732	-	
733	rac	
734	+	
735	-	

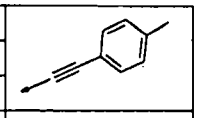
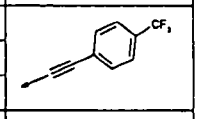
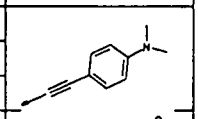
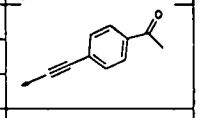


No.	Racemic or enantiomer	R3
736	rac	
737	-	
738	+	
739	rac	
740	+	
741	-	
742	rac	
743	+	
744	-	
745	rac	
746	+	
747	-	
748	rac	
749	+	
750	-	
751	rac	
752	+	
753	-	
754	rac	
755	+	
756	-	
757	rac	
758	+	
759	-	
760	rac	
761	+	
762	-	

763	rac	
764	+	
765	-	
766	rac	
767	+	
768	-	
769	rac	
770	+	
771	-	
772	rac	
773	+	
774	-	
775	rac	
776	+	
777	-	
778	rac	
779	+	
780	-	
781	rac	
782	+	
783	-	
784	rac	
785	+	
786	-	
787	rac	
788	+	
789	-	
790	rac	
791	+	
792	-	
793	rac	
794	+	
795	-	
796	rac	
797	+	
798	-	

No.	Racemic or enantiomer	R3
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	
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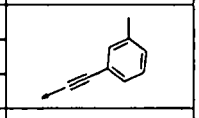
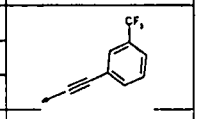
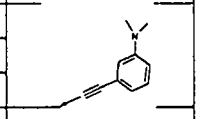
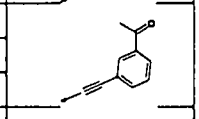
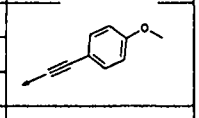
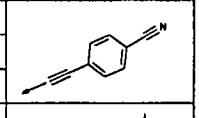
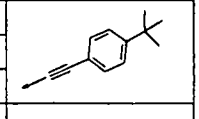
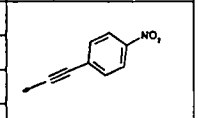
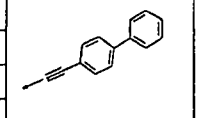
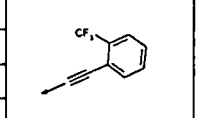
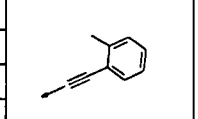
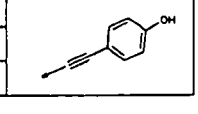
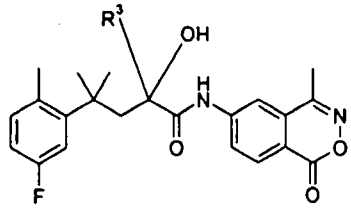
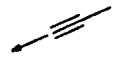
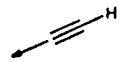
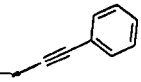
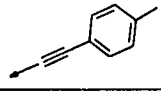
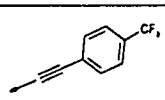
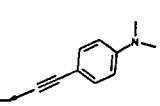
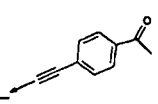
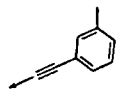
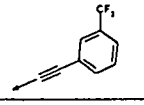
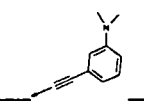
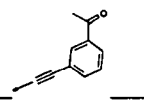
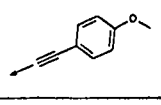
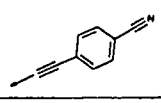
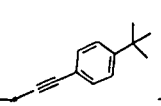
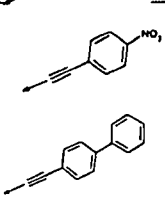
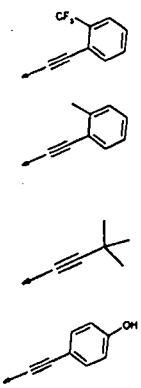
822	-	
823	rac	
824	+	
825	-	
826	rac	
827	+	
828	-	
829	rac	
830	+	
831	-	
832	rac	
833	+	
834	-	
835	rac	
836	+	
837	-	
838	rac	
839	+	
840	-	
841	rac	
842	+	
843	-	
844	rac	
845	+	
846	-	
847	rac	
848	+	
849	-	
850	rac	
851	+	
852	-	
853	rac	
854	+	
855	-	
856	rac	
857	+	
858	-	
859	rac	
860	+	
861	-	

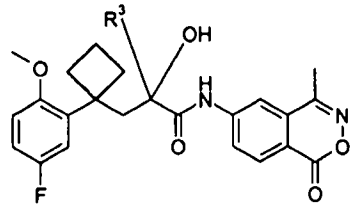


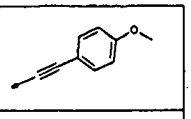
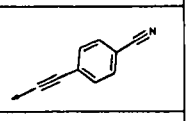
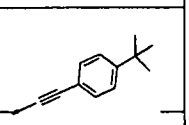
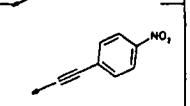
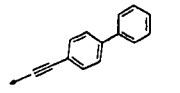
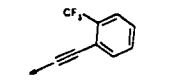
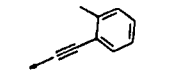
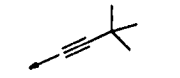
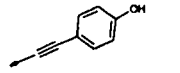
No.	Racemic or enantiomer	R3
862	rac	
863	-	
864	+	
865	rac	
866	+	
867	-	
868	rac	
869	+	
870	-	
871	rac	
872	+	
873	-	
874	rac	
875	+	
876	-	
877	rac	
878	+	
879	-	
880	rac	
881	+	
882	-	
883	rac	
884	+	
885	-	
886	rac	
887	+	
888	-	
889	rac	
890	+	
891	-	
892	rac	
893	+	
894	-	
895	rac	
896	+	
897	-	
898	rac	
899	+	
900	-	
901	rac	
902	+	
903	-	
904	rac	
905	+	
906	-	
907	rac	
908	+	
909	-	
910	rac	
911	+	

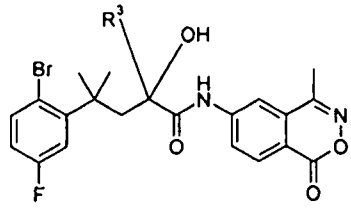
912	-
913	rac
914	+
915	-
916	rac
917	+
918	-
919	rac
920	+
921	-
922	rac
923	+
924	-

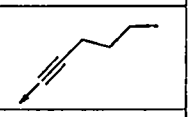
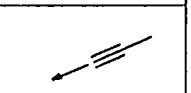
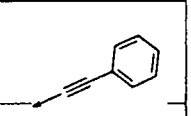
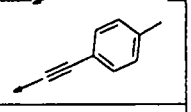
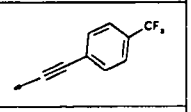
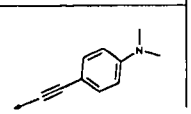


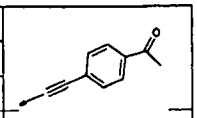
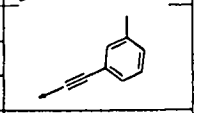
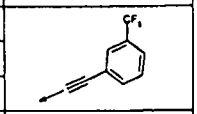
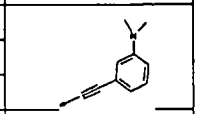
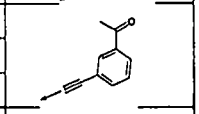
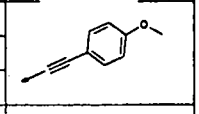
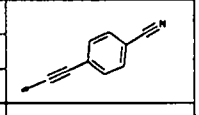
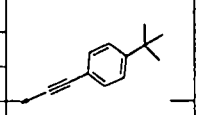
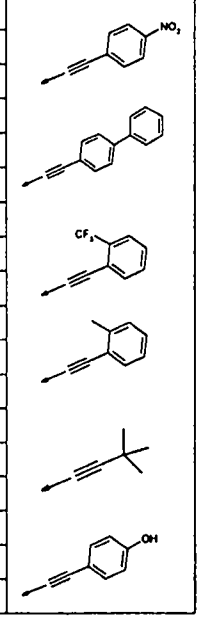
No.	Racemic or enantiomer	R3
925	rac	
926	-	
927	+	
928	rac	
929	+	
930	-	
931	rac	
932	+	
933	-	
934	rac	
935	+	
936	-	
937	rac	
938	+	
939	-	
940	rac	
941	+	
942	-	
943	rac	
944	+	
945	-	
946	rac	
947	+	
948	-	
949	rac	
950	+	
951	-	
952	rac	
953	+	
954	-	
955	rac	
956	+	
957	-	
958	rac	
959	+	
960	-	

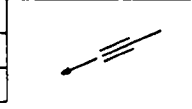


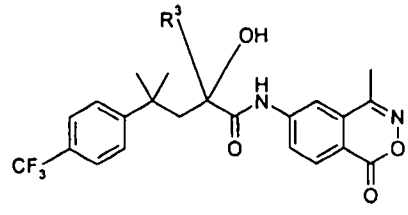
961	rac	
962	+	
963	-	
964	rac	
965	+	
966	-	
967	rac	
968	+	
969	-	
970	rac	
971	+	
972	-	
973	rac	
974	+	
975	-	
976	rac	
977	+	
978	-	
979	rac	
980	+	
981	-	
982	rac	
983	+	
984	-	
985	rac	
986	+	
987	-	

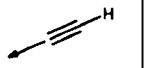
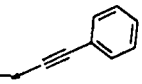
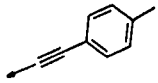
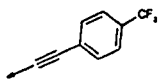
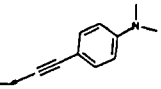
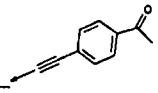
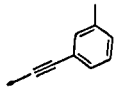
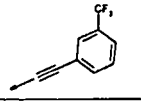
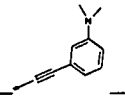
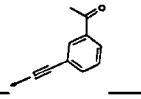
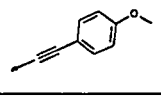
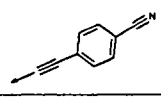
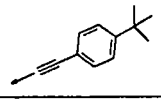
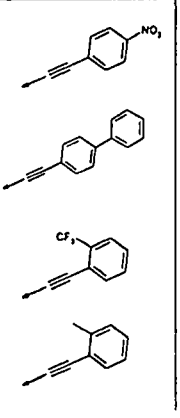


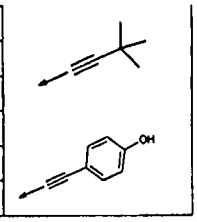
No.	Racemic or enantiomer	R3
988	rac	
989	-	
990	+	
991	rac	
992	+	
993	-	
994	rac	
995	+	
996	-	
997	rac	
998	+	
999	-	
1000	rac	
1001	+	
1002	-	
1003	rac	
1004	+	
1005	-	
1006	rac	
1007	+	
1008	-	

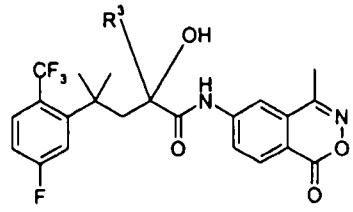
1009	rac	
1010	+	
1011	-	
1012	rac	
1013	+	
1014	-	
1015	rac	
1016	+	
1017	-	
1018	rac	
1019	+	
1020	-	
1021	rac	
1022	+	
1023	-	
1024	rac	
1025	+	
1026	-	
1027	rac	
1028	+	
1029	-	
1030	rac	
1031	+	
1032	-	
1033	rac	
1034	+	
1035	-	
1036	rac	
1037	+	
1038	-	
1039	rac	
1040	+	
1041	-	
1042	rac	
1043	+	
1044	-	
1045	rac	
1046	+	
1047	-	
1048	rac	
1049	+	
1050	-	

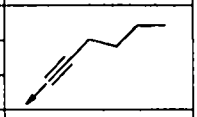
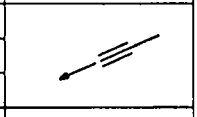
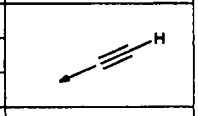
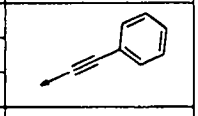
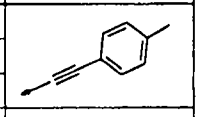
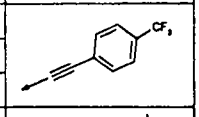
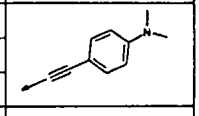
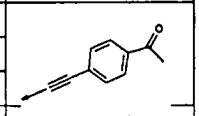
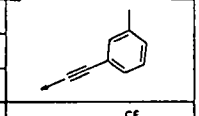
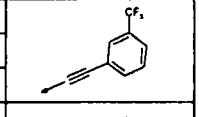
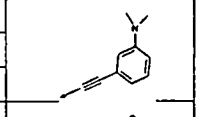
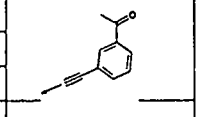
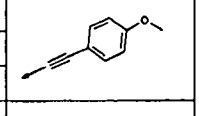
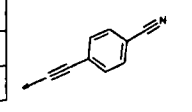
No.	Racemic or enantiomer	R3
1051	rac	
1052	-	
1053	+	
1054	rac	
1055	+	
1056	-	

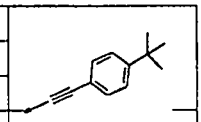
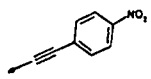
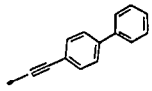
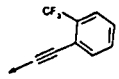
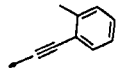
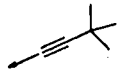
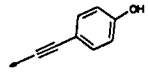


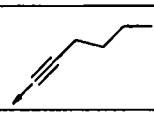
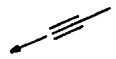
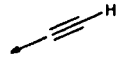
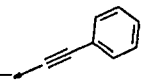
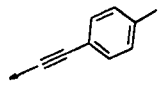
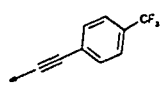
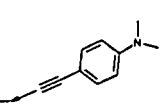
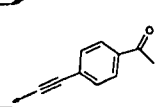
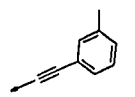
1057	rac	
1058	+	
1059	-	
1060	rac	
1061	+	
1062	-	
1063	rac	
1064	+	
1065	-	
1066	rac	
1067	+	
1068	-	
1069	rac	
1070	+	
1071	-	
1072	rac	
1073	+	
1074	-	
1075	rac	
1076	+	
1077	-	
1078	rac	
1079	+	
1080	-	
1081	rac	
1082	+	
1083	-	
1084	rac	
1085	+	
1086	-	
1087	rac	
1088	+	
1089	-	
1090	rac	
1091	+	
1092	-	
1093	rac	
1094	+	
1095	-	
1096	rac	
1097	+	
1098	-	
1099	rac	
1100	+	
1101	-	
1102	rac	
1103	+	
1104	-	
1105	rac	
1106	+	
1107	-	

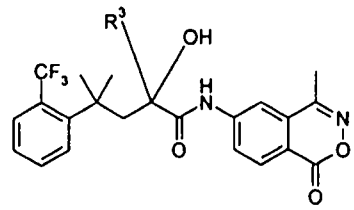
1108	rac	
1109	+	
1110	-	
1111	rac	
1112	+	
1113	-	

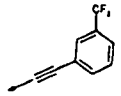
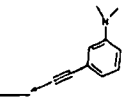
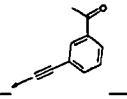
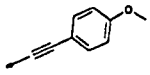
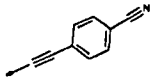
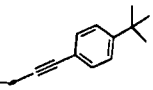
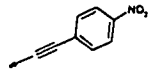
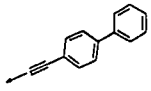
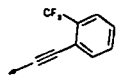
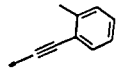
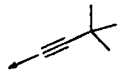
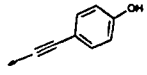


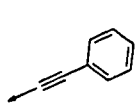
No.	Racemic or enantiomer	R3
1114	rac	
1115	-	
1116	+	
1117	rac	
1118	+	
1119	-	
1120	rac	
1121	+	
1122	-	
1123	rac	
1124	+	
1125	-	
1126	rac	
1127	+	
1128	-	
1129	rac	
1130	+	
1131	-	
1132	rac	
1133	+	
1134	-	
1135	rac	
1136	+	
1137	-	
1138	rac	
1139	+	
1140	-	
1141	rac	
1142	+	
1143	-	
1144	rac	
1145	+	
1146	-	
1147	rac	
1148	+	
1149	-	
1150	rac	
1151	+	
1152	-	
1153	rac	
1154	+	
1155	-	

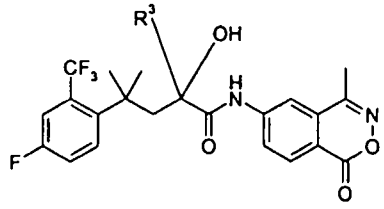
1156	rac	
1157	+	
1158	-	
1159	rac	
1160	+	
1161	-	
1162	rac	
1163	+	
1164	-	
1165	rac	
1166	+	
1167	-	
1168	rac	
1169	+	
1170	-	
1171	rac	
1172	+	
1173	-	
1174	rac	
1175	+	
1176	-	

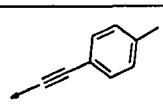
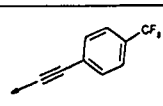
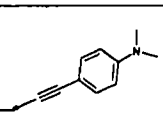
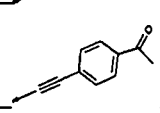
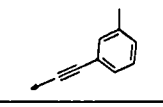
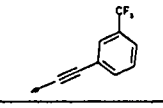
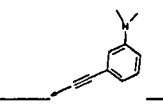
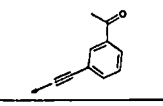
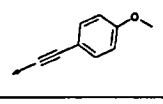
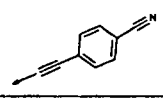
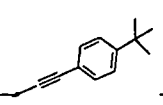
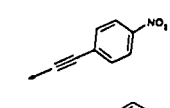
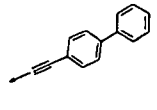
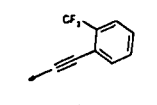
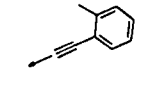
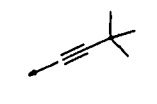
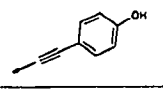
No.	Racemic or enantiomer	R3
1177	rac	
1178	-	
1179	+	
1180	rac	
1181	+	
1182	-	
1183	rac	
1184	+	
1185	-	
1186	rac	
1187	+	
1188	-	
1189	rac	
1190	+	
1191	-	
1192	rac	
1193	+	
1194	-	
1195	rac	
1196	+	
1197	-	
1198	rac	
1199	+	
1200	-	
1202	rac	
1202	+	
1203	-	

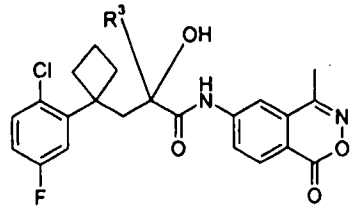


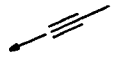
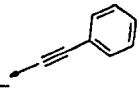
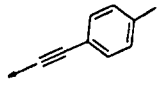
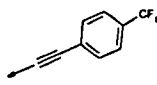
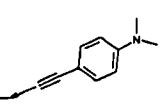
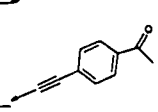
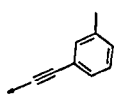
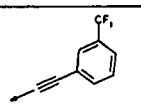
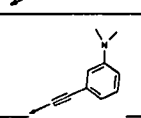
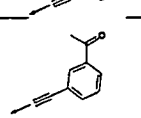
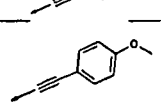
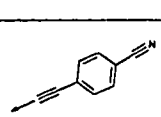
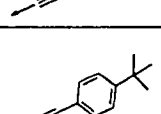
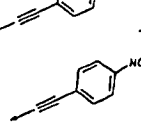
1204	rac	
1205	+	
1206	-	
1207	rac	
1208	+	
1209	-	
1210	rac	
1211	+	
1212	-	
1213	rac	
1214	+	
1215	-	
1216	rac	
1217	+	
1218	-	
1219	rac	
1220	+	
1221	-	
1222	rac	
1223	+	
1224	-	
1225	rac	
1226	+	
1227	-	
1228	rac	
1229	+	
1230	-	
1231	rac	
1232	+	
1233	-	
1234	rac	
1235	+	
1236	-	
1237	rac	
1238	+	
1239	-	

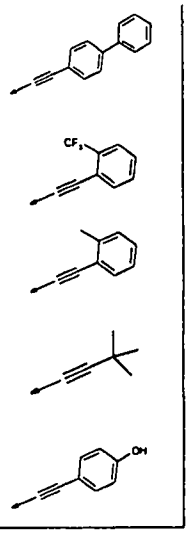
No.	Racemic or enantiomer	R3
1240	rac	
1241	-	
1242	+	
1243	rac	
1244	+	
1245	-	
1246	rac	
1247	+	
1248	-	
1249	rac	
1250	+	
1251	-	

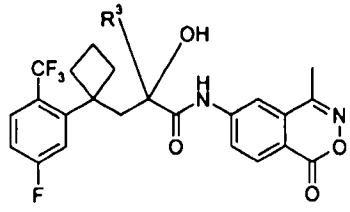


1252	rac	
1253	+	
1254	-	
1255	rac	
1256	+	
1257	-	
1258	rac	
1259	+	
1260	-	
1261	rac	
1262	+	
1263	-	
1264	rac	
1265	+	
1266	-	
1267	rac	
1268	+	
1269	-	
1270	rac	
1271	+	
1272	-	
1273	rac	
1274	+	
1275	-	
1276	rac	
1277	+	
1278	-	
1279	rac	
1280	+	
1281	-	
1282	rac	
1283	+	
1284	-	
1285	rac	
1286	+	
1287	-	
1288	rac	
1289	+	
1290	-	
1291	rac	
1292	+	
1293	-	
1294	rac	
1295	+	
1296	-	
1297	rac	
1298	+	
1299	-	
1300	rac	
1301	+	
1302	-	

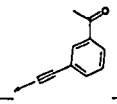
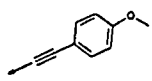
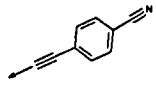
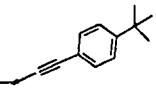
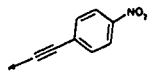
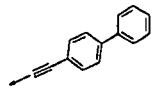
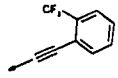
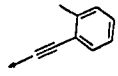
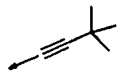
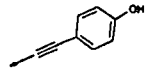


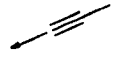
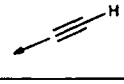
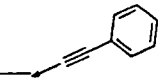
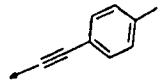
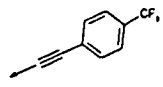
No.	Racemic or enantiomer	R3
1303	rac	
1304	-	
1305	+	
1306	rac	
1307	+	
1308	-	
1309	rac	
1310	+	
1311	-	
1312	rac	
1313	+	
1314	-	
1315	rac	
1316	+	
1317	-	
1318	rac	
1319	+	
1320	-	
1321	rac	
1322	+	
1323	-	
1324	rac	
1325	+	
1326	-	
1327	rac	
1328	+	
1329	-	
1330	rac	
1331	+	
1332	-	
1333	rac	
1334	+	
1335	-	
1336	rac	
1337	+	
1338	-	
1339	rac	
1340	+	
1341	-	
1342	rac	
1343	+	
1344	-	
1345	rac	
1346	+	
1347	-	
1348	rac	
1349	+	
1350	-	

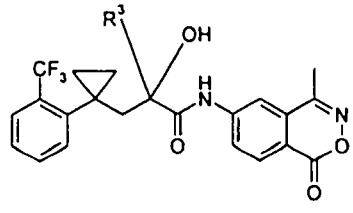
1351	rac	
1352	+	
1353	-	
1354	rac	
1355	+	
1356	-	
1357	rac	
1358	+	
1359	-	
1360	rac	
1361	+	
1362	-	
1362	rac	
1364	+	
1365	-	

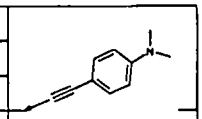
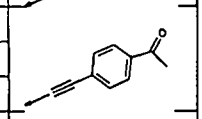
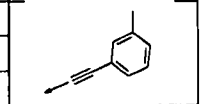
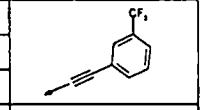
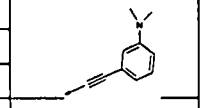
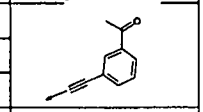
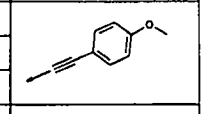
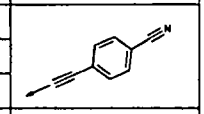
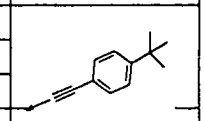


No.	Racemic or enantiomer	R3
1366	rac	
1367	-	
1368	+	
1369	rac	
1370	+	
1371	-	
1372	rac	
1373	+	
1374	-	
1375	rac	
1376	+	
1377	-	
1378	rac	
1379	+	
1380	-	
1381	rac	
1382	+	
1383	-	
1384	rac	
1385	+	
1386	-	
1387	rac	
1388	+	
1389	-	
1390	rac	
1391	+	
1392	-	
1393	rac	
1394	+	
1395	-	
1396	rac	
1397	+	
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	-	

No.	Racemic or enantiomer	R3
1429	rac	
1430	-	
1431	+	
1432	rac	
1433	+	
1434	-	
1435	rac	
1436	+	
1437	-	
1438	rac	
1439	+	
1440	-	
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	
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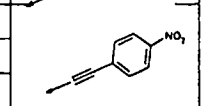
1473	-	
1474	rac	
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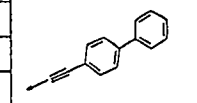
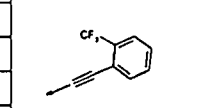
1477	rac	
1478	+	
1479	-	
1480	rac	
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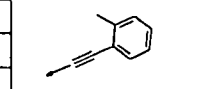
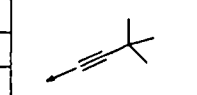
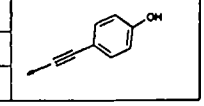
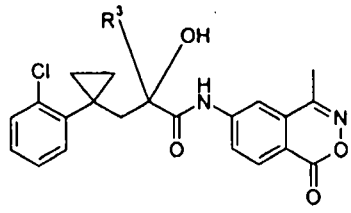
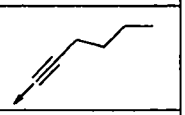
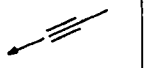
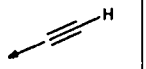
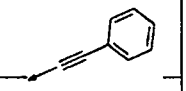
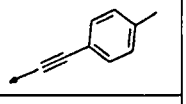
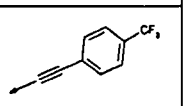
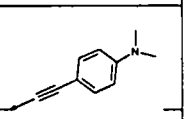
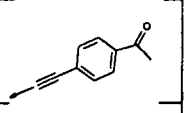
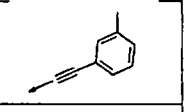
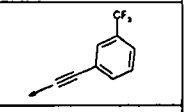
1483	rac	
1484	+	
1485	-	
1486	rac	
1487	+	
1488	-	
1489	rac	
1490	+	
1491	-	



No.	Racemic or enantiomer	R3
1492	rac	
1493	-	
1494	+	
1495	rac	
1496	+	
1497	-	
1498	rac	
1499	+	
1500	-	
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	
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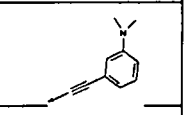
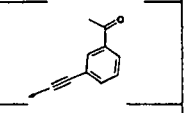
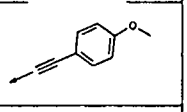
1521	-	
1522	rac	
1523	+	
1524	-	
1525	rac	
1526	+	
1527	-	
1528	rac	
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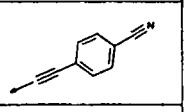
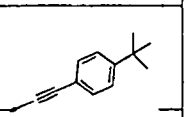
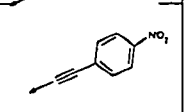
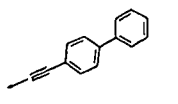
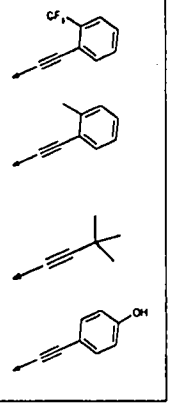
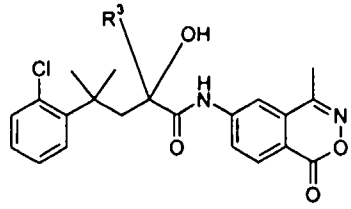
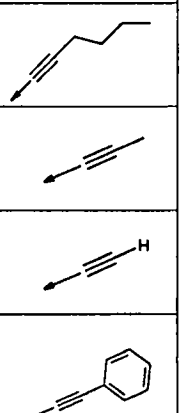
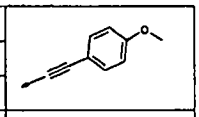
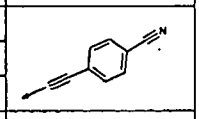
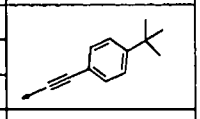
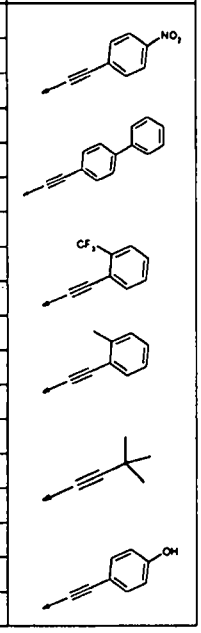
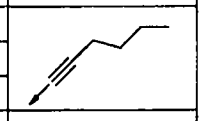
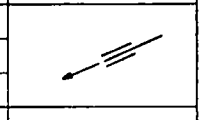
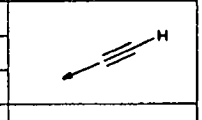
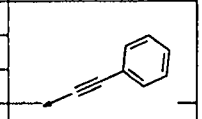
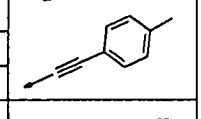
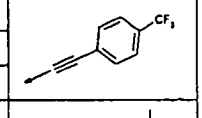
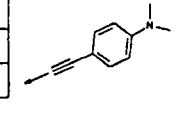
1530	-	
1531	rac	
1532	+	
1533	-	
1534	rac	
1535	+	
1536	-	
1537	rac	
1538	+	
1539	-	
1540	rac	
1541	+	
1542	-	

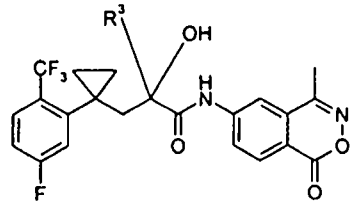
1543	rac	
1544	+	
1545	-	
1546	rac	
1547	+	
1548	-	
1549	rac	
1550	+	
1551	-	
1552	rac	
1553	+	
1554	-	

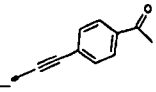
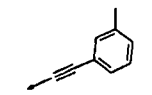
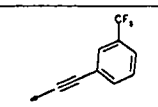
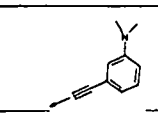
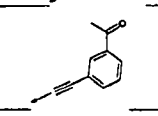
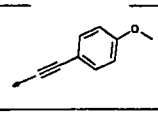
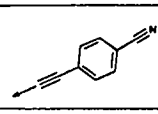
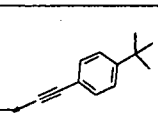
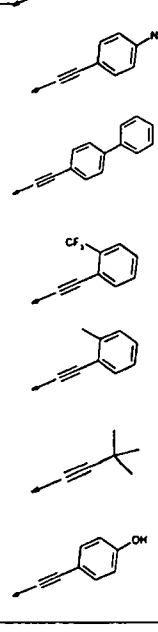


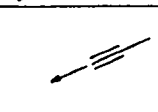
No.	Racemic or enantiomer	R3
1555	rac	
1556	-	
1557	+	
1558	rac	
1559	+	
1560	-	
1561	rac	
1562	+	
1563	-	
1564	rac	
1565	+	
1566	-	
1567	rac	
1568	+	
1569	-	
1570	rac	
1571	+	
1572	-	
1573	rac	
1574	+	
1575	-	
1576	rac	
1577	+	
1578	-	
1579	rac	
1580	+	
1581	-	
1582	rac	
1583	+	
1584	-	
1585	rac	
1586	+	
1587	-	
1588	rac	
1589	+	
1590	-	

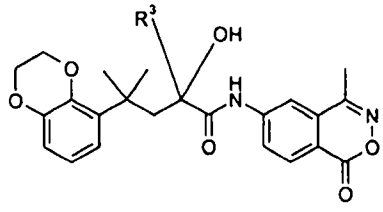
1591	rac	
1592	+	
1593	-	
1594	rac	
1595	+	
1596	-	
1597	rac	
1598	+	
1599	-	
1600	rac	
1601	+	
1602	-	
1603	rac	
1604	+	
1605	-	
1606	rac	
1607	+	
1608	-	
1609	rac	
1610	+	
1611	-	
1612	rac	
1613	+	
1614	-	
1615	rac	
1616	+	
1617	-	

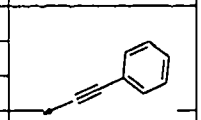
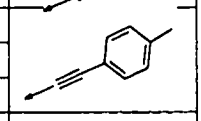
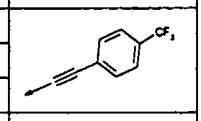
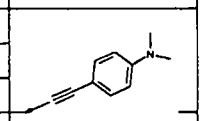
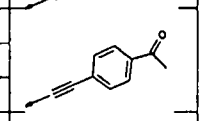
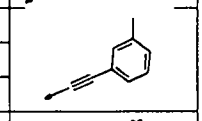
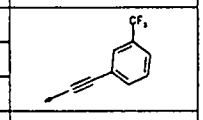
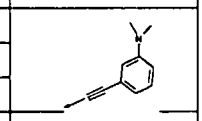
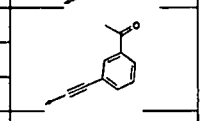
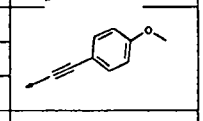
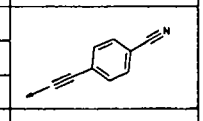
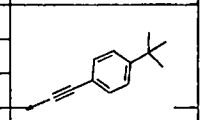
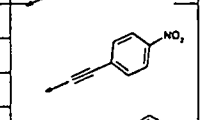
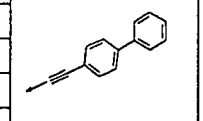
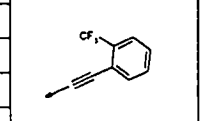
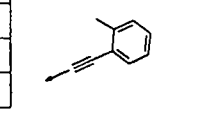
No.	Racemic or enantiomer	R3
1618	rac	
1619	-	
1620	+	
1621	rac	
1622	+	
1623	-	
1624	rac	
1625	+	
1626	-	
1627	rac	
1628	+	
1629	-	
1630	rac	
1631	+	
1632	-	
1633	rac	
1634	+	
1635	-	
1636	rac	
1637	+	
1638	-	

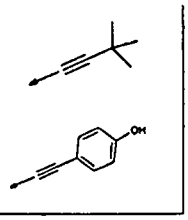


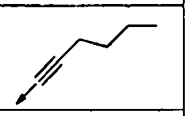
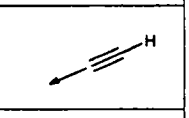
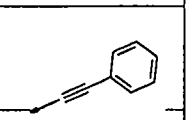
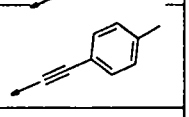
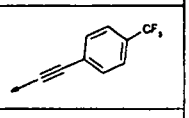
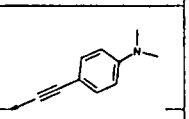
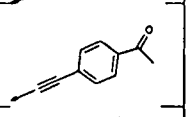
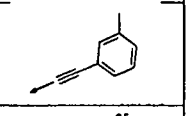
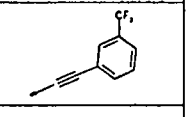
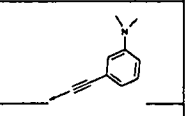
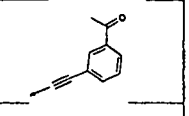
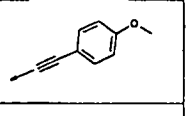
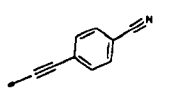
1639	rac	
1640	+	
1641	-	
1642	rac	
1643	+	
1644	-	
1645	rac	
1646	+	
1647	-	
1648	rac	
1649	+	
1650	-	
1651	rac	
1652	+	
1653	-	
1654	rac	
1655	+	
1656	-	
1657	rac	
1658	+	
1659	-	
1660	rac	
1661	+	
1662	-	
1663	rac	
1664	+	
1665	-	
1666	rac	
1667	+	
1668	-	
1669	rac	
1670	+	
1671	-	
1672	rac	
1673	+	
1674	-	
1675	rac	
1676	+	
1677	-	
1678	rac	
1679	+	
1680	-	

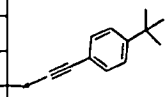
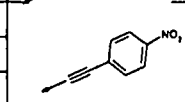
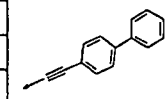
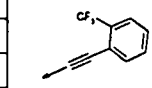
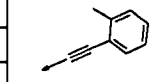
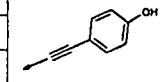
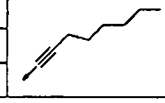
No.	Racemic or enantiomer	R3
1681	rac	
1682	-	
1683	+	
1684	rac	
1685	+	
1686	-	

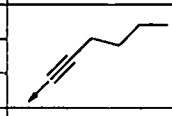
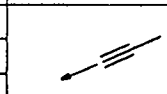
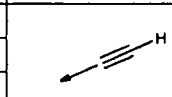
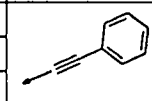
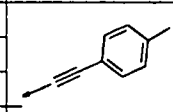
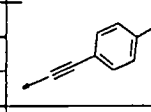
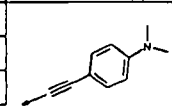


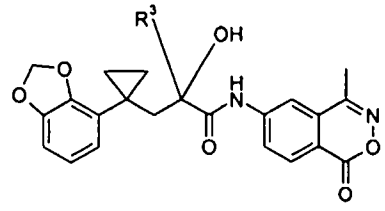
1687	rac	
1688	+	
1689	-	
1690	rac	
1691	+	
1692	-	
1693	rac	
1694	+	
1695	-	
1696	rac	
1697	+	
1698	-	
1699	rac	
1700	+	
1701	-	
1702	rac	
1703	+	
1704	-	
1705	rac	
1706	+	
1707	-	
1708	rac	
1709	+	
1710	-	
1711	rac	
1712	+	
1713	-	
1714	rac	
1715	+	
1716	-	
1717	rac	
1718	+	
1719	-	
1720	rac	
1721	+	
1722	-	
1723	rac	
1724	+	
1725	-	
1726	rac	
1727	+	
1728	-	
1729	rac	
1730	+	
1731	-	
1732	rac	
1733	+	
1734	-	
1735	rac	
1736	+	
1737	-	

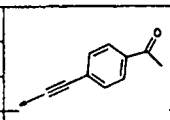
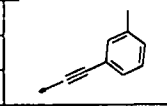
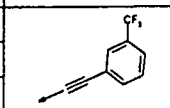
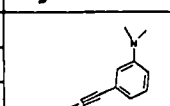
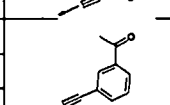
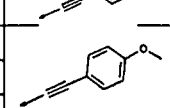
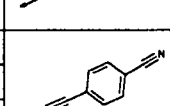
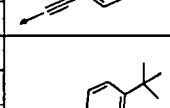
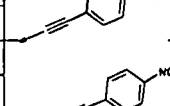
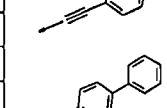
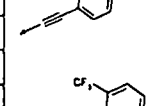
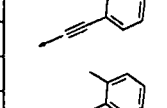
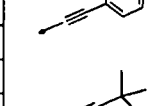
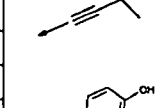
1738	rac	
1739	+	
1740	-	
1741	rac	
1742	+	
1743	-	

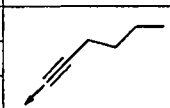
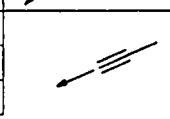
No.	Racemic or enantiomer	R3
1744	rac	
1745	-	
1746	+	
1747	rac	
1748	+	
1749	-	
1750	rac	
1751	+	
1752	-	
1753	rac	
1754	+	
1755	-	
1756	rac	
1757	+	
1758	-	
1759	rac	
1760	+	
1761	-	
1762	rac	
1763	+	
1764	-	
1765	rac	
1766	+	
1767	-	
1768	rac	
1769	+	
1770	-	
1771	rac	
1772	+	
1773	-	
1774	rac	
1775	+	
1776	-	
1777	rac	
1778	+	
1779	-	
1780	rac	
1781	+	
1782	-	
1783	rac	
1784	+	
1785	-	

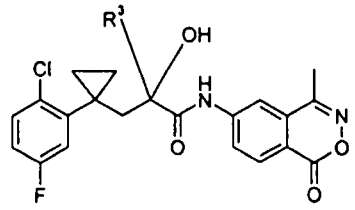
1786	rac	
1787	+	
1788	-	
1789	rac	
1790	+	
1791	-	
1792	rac	
1793	+	
1794	-	
1795	rac	
1796	+	
1797	-	
1798	rac	
1799	+	
1800	-	
1801	rac	
1802	+	
1803	-	
1804	rac	
1805	+	
1806	-	
1807	rac	
1808	+	
1809	-	
1810	rac	
1811	+	
1812	-	

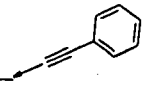
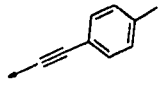
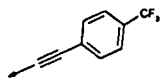
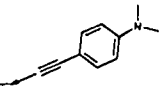
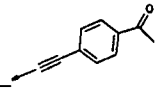
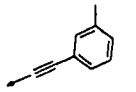
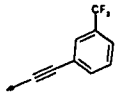
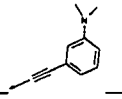
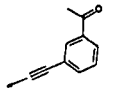
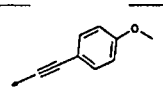
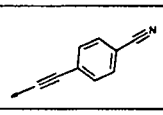
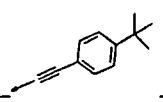
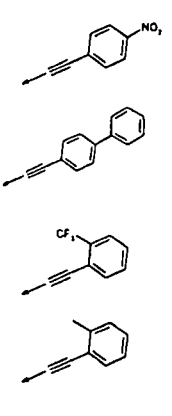
No.	Racemic or enantiomer	R3
1813	rac	
1814	-	
1815	+	
1816	rac	
1817	+	
1818	-	
1819	rac	
1820	+	
1821	-	
1822	rac	
1823	+	
1824	-	
1825	rac	
1826	+	
1827	-	
1828	rac	
1829	+	
1830	-	
1831	rac	
1832	+	
1833	-	



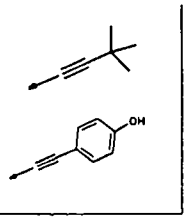
1834	rac	
1835	+	
1836	-	
1837	rac	
1838	+	
1839	-	
1840	rac	
1841	+	
1842	-	
1843	rac	
1844	+	
1845	-	
1846	rac	
1847	+	
1848	-	
1849	rac	
1850	+	
1851	-	
1852	rac	
1853	+	
1854	-	
1855	rac	
1856	+	
1857	-	
1858	rac	
1859	+	
1860	-	
1861	rac	
1862	+	
1863	-	
1864	rac	
1865	+	
1866	-	
1867	rac	
1868	+	
1869	-	
1870	rac	
1871	+	
1872	-	
1873	rac	
1874	+	
1875	-	

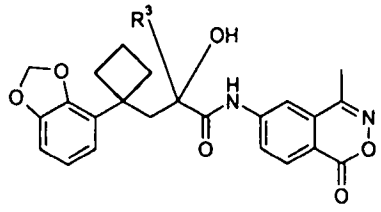
No.	Racemic or enantiomer	R3
1876	rac	
1877	-	
1878	+	
1879	rac	
1880	+	
1881	-	

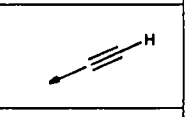
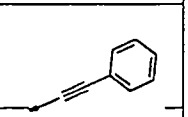
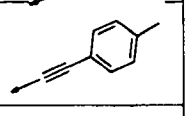
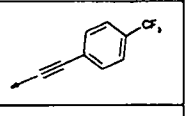
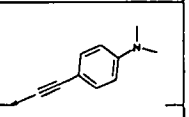
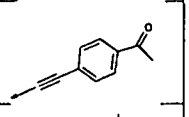
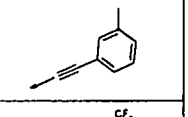
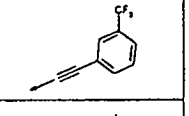
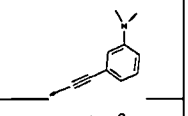
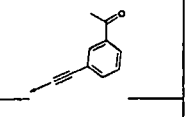
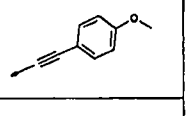
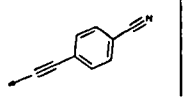


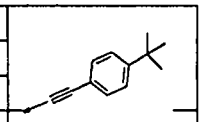
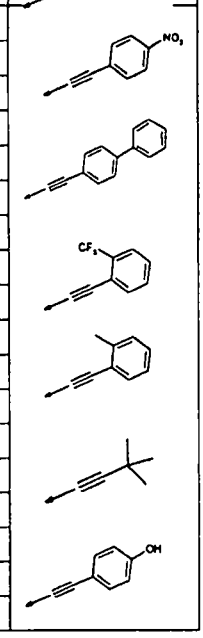
1882	rac	
1883	+	
1884	-	
1885	rac	
1886	+	
1887	-	
1888	rac	
1889	+	
1890	-	
1891	rac	
1892	+	
1893	-	
1894	rac	
1895	+	
1896	-	
1897	rac	
1898	+	
1899	-	
1900	rac	
1901	+	
1902	-	
1903	rac	
1904	+	
1905	-	
1906	rac	
1907	+	
1908	-	
1909	rac	
1910	+	
1911	-	
1912	rac	
1913	+	
1914	-	
1915	rac	
1916	+	
1917	-	
1918	rac	
1919	+	
1920	-	
1921	rac	
1922	+	
1923	-	
1924	rac	
1925	+	
1926	-	
1927	rac	
1928	+	
1929	-	
1930	rac	
1931	+	
1932	-	

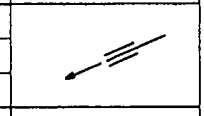
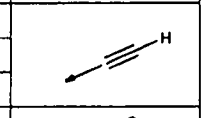
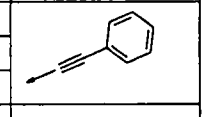
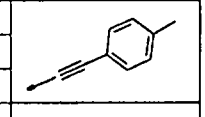
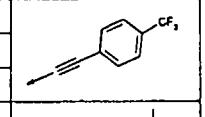
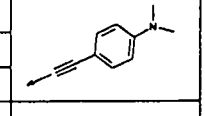
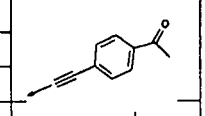
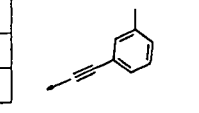
150

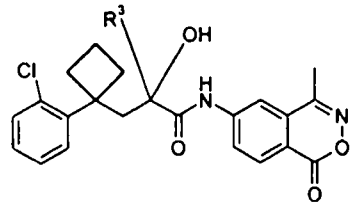
1933	rac	
1934	+	
1935	-	
1936	rac	
1937	+	
1938	-	

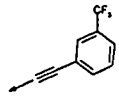
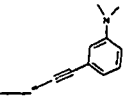
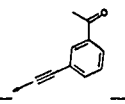
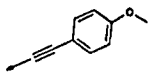
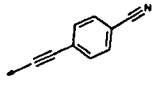
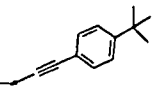
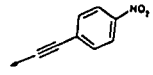
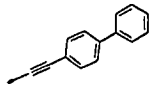
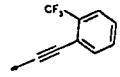
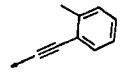
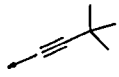
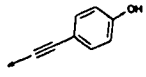


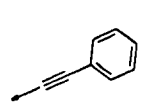
No.	Racemic or enantiomer	R3
1939	rac	
1940	-	
1941	+	
1942	rac	
1943	+	
1944	-	
1945	rac	
1946	+	
1947	-	
1948	rac	
1949	+	
1950	-	
1951	rac	
1952	+	
1953	-	
1954	rac	
1955	+	
1956	-	
1957	rac	
1958	+	
1959	-	
1960	rac	
1961	+	
1962	-	
1963	rac	
1964	+	
1965	-	
1966	rac	
1967	+	
1968	-	
1969	rac	
1970	+	
1971	-	
1972	rac	
1973	+	
1974	-	
1975	rac	
1976	+	
1977	-	
1978	rac	
1979	+	
1980	-	

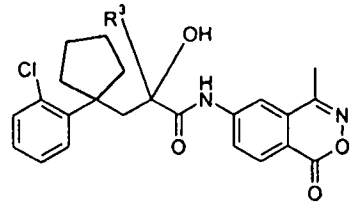
1981	rac	
1982	+	
1983	-	
1984	rac	
1985	+	
1986	-	
1987	rac	
1988	+	
1989	-	
1990	rac	
1991	+	
1992	-	
1993	rac	
1994	+	
1995	-	
1996	rac	
1997	+	
1998	-	
1999	rac	
2000	+	
2001	-	

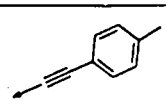
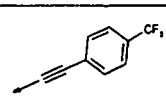
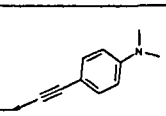
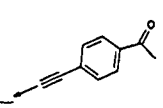
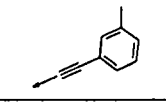
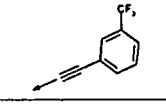
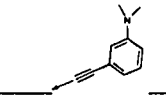
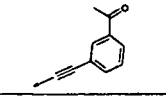
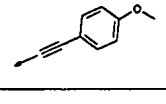
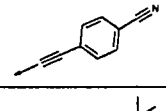
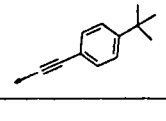
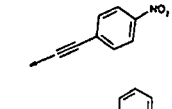
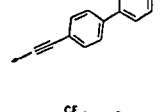
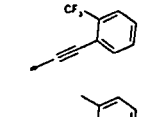
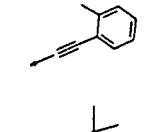
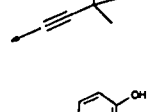
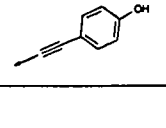
No.	Racemic or enantiomer	R3
2002	rac	
2003	-	
2004	+	
2005	rac	
2006	+	
2007	-	
2008	rac	
2009	+	
2010	-	
2011	rac	
2012	+	
2013	-	
2014	rac	
2015	+	
2016	-	
2017	rac	
2018	+	
2019	-	
2020	rac	
2021	+	
2022	-	
2023	rac	
2024	+	
2025	-	
2026	rac	
2027	+	
2028	-	

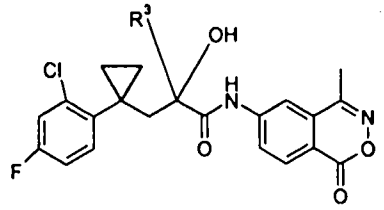


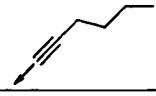
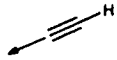
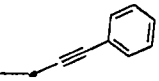
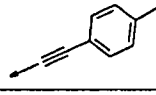
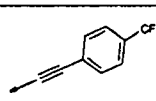
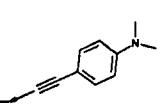
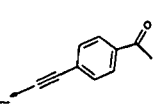
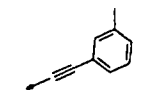
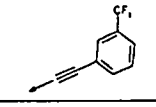
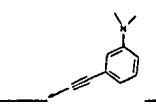
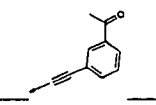
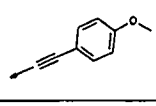
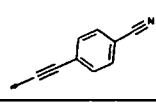
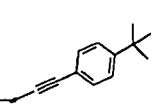
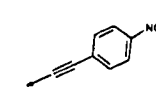
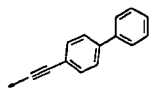
2029	rac	
2030	+	
2031	-	
2032	rac	
2033	+	
2034	-	
2035	rac	
2036	+	
2037	-	
2038	rac	
2039	+	
2040	-	
2041	rac	
2042	+	
2043	-	
2044	rac	
2045	+	
2046	-	
2047	rac	
2048	+	
2049	-	
2050	rac	
2051	+	
2052	-	
2053	rac	
2054	+	
2055	-	
2056	rac	
2057	+	
2058	-	
2059	rac	
2060	+	
2061	-	
2062	rac	
2063	+	
2064	-	

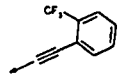
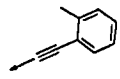
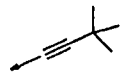
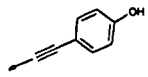
No.	Racemic or enantiomer	R3
2065	rac	
2066	-	
2067	+	
2068	rac	
2069	+	
2070	-	
2071	rac	
2072	+	
2073	-	
2074	rac	
2075	+	
2076	-	

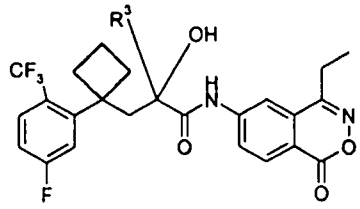


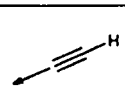
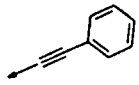
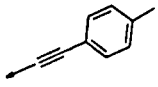
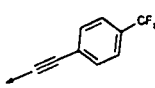
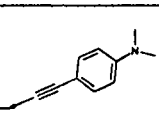
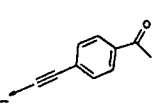
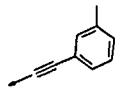
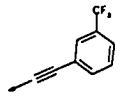
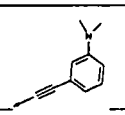
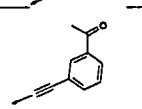
2077	rac	
2078	+	
2079	-	
2080	rac	
2081	+	
2082	-	
2083	rac	
2084	+	
2085	-	
2086	rac	
2087	+	
2088	-	
2089	rac	
2090	+	
2091	-	
2092	rac	
2093	+	
2094	-	
2095	rac	
2096	+	
2097	-	
2098	rac	
2099	+	
2100	-	
2101	rac	
2102	+	
2103	-	
2104	rac	
2105	+	
2106	-	
2107	rac	
2108	+	
2109	-	
2110	rac	
2111	+	
2112	-	
2113	rac	
2114	+	
2115	-	
2116	rac	
2117	+	
2118	-	
2119	rac	
2120	+	
2121	-	
2122	rac	
2123	+	
2124	-	
2125	rac	
2126	+	
2127	-	

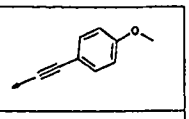
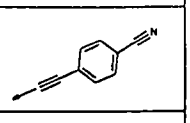
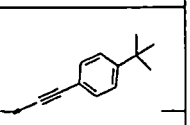
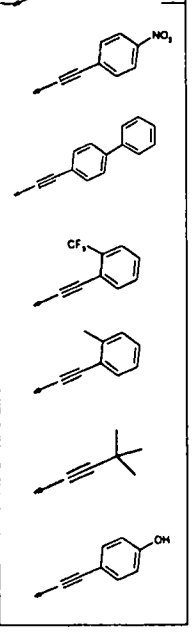


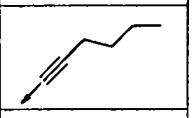
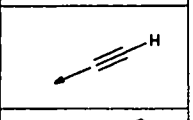
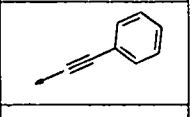
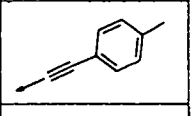
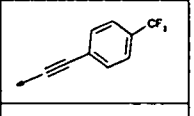
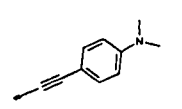
No.	Racemic or enantiomer	R3
2128	rac	
2129	-	
2130	+	
2131	rac	
2132	+	
2133	-	
2134	rac	
2135	+	
2136	-	
2137	rac	
2138	+	
2139	-	
2140	rac	
2141	+	
2142	-	
2143	rac	
2144	+	
2145	-	
2146	rac	
2147	+	
2148	-	
2149	rac	
2150	+	
2151	-	
2152	rac	
2153	+	
2154	-	
2155	rac	
2156	+	
2157	-	
2158	rac	
2159	+	
2160	-	
2161	rac	
2163	+	
2163	-	
2164	rac	
2165	+	
2166	-	
2167	rac	
2168	+	
2169	-	
2170	rac	
2171	+	
2172	-	
2173	rac	
2174	+	
2175	-	
2176	rac	
2177	+	
2178	-	

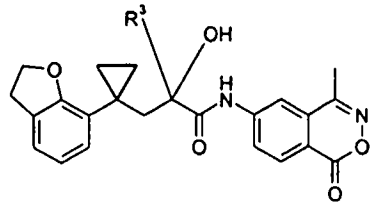
2179	rac	
2180	+	
2181	-	
2182	rac	
2183	+	
2184	-	
2185	rac	
2186	+	
2187	-	
2188	rac	
2189	+	
2190	-	

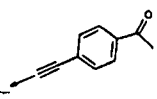
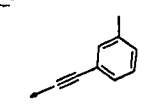
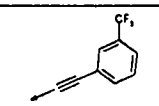
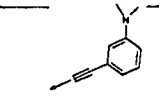
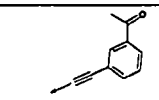
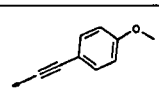
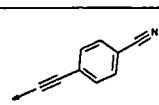
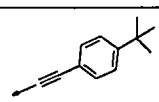
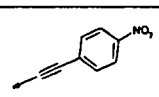
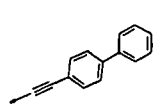
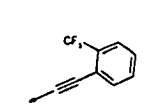
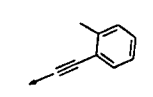
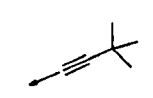
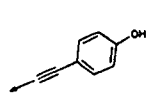


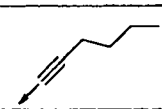
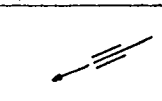
No.	Racemic or enantiomer	R3
2191	rac	
2192	-	
2193	+	
2194	rac	
2195	+	
2196	-	
2197	rac	
2198	+	
2199	-	
2200	rac	
2201	+	
2202	-	
2203	rac	
2204	+	
2205	-	
2206	rac	
2207	+	
2208	-	
2209	rac	
2210	+	
2211	-	
2212	rac	
2213	+	
2214	-	
2215	rac	
2216	+	
2217	-	
2218	rac	
2219	+	
2220	-	
2221	rac	
2222	+	
2223	-	
2224	rac	
2225	+	
2226	-	

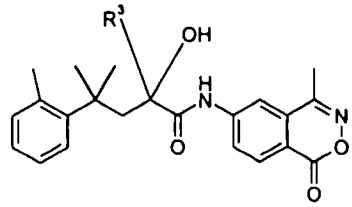
2227	rac	
2228	+	
2229	-	
2230	rac	
2231	+	
2232	-	
2233	rac	
2234	+	
2235	-	
2236	rac	
2237	+	
2238	-	
2239	rac	
2240	+	
2241	-	
2242	rac	
2243	+	
2244	-	
2245	rac	
2246	+	
2247	-	
2248	rac	
2249	+	
2250	-	
2251	rac	
2252	+	
2253	-	

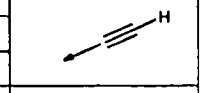
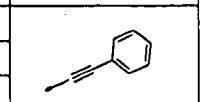
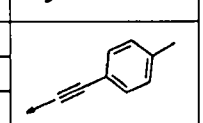
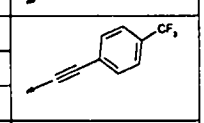
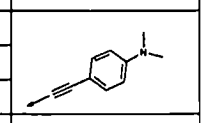
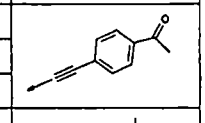
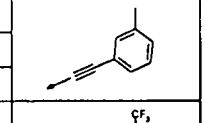
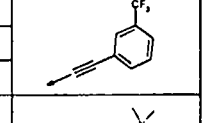
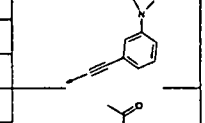
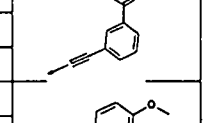
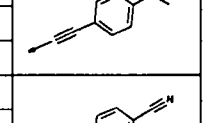
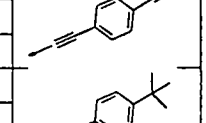
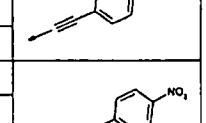
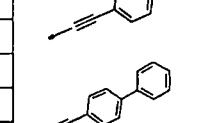
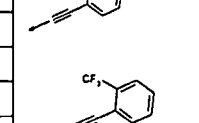
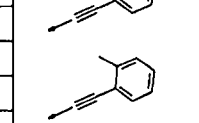
No.	Racemic or enantiomer	R3
2254	rac	
2255	-	
2256	+	
2257	rac	
2258	+	
2259	-	
2260	rac	
2261	+	
2262	-	
2263	rac	
2264	+	
2265	-	
2266	rac	
2267	+	
2268	-	
2269	rac	
2270	+	
2271	-	
2272	rac	
2273	+	
2274	-	

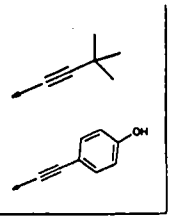


2273	rac	
2276	+	
2277	-	
2278	rac	
2279	+	
2280	-	
2281	rac	
2282	+	
2283	-	
2284	rac	
2285	+	
2286	-	
2287	rac	
2288	+	
2289	-	
2290	rac	
2291	+	
2292	-	
2293	rac	
2294	+	
2295	-	
2296	rac	
2297	+	
2298	-	
2299	rac	
2300	+	
2301	-	
2302	rac	
2303	+	
2304	-	
2305	rac	
2306	+	
2307	-	
2308	rac	
2309	+	
2310	-	
2311	rac	
2312	+	
2313	-	
2314	rac	
2315	+	
2316	-	

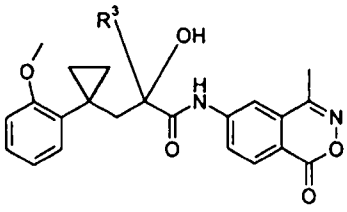
No.	Racemic or enantiomer	R3
2317	rac	
2318	-	
2319	+	
2320	rac	
2321	+	
2322	-	

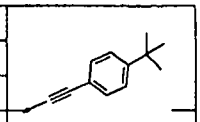
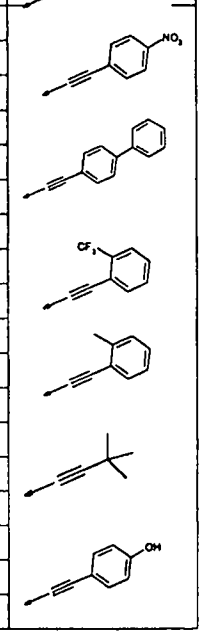


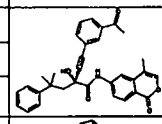
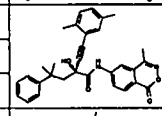
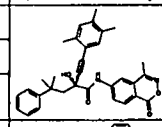
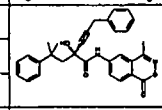
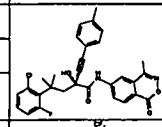
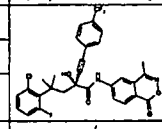
2323	rac	
2324	+	
2325	-	
2326	rac	
2327	+	
2328	-	
2329	rac	
2330	+	
2331	-	
2332	rac	
2333	+	
2334	-	
2335	rac	
2336	+	
2337	-	
2338	rac	
2339	+	
2340	-	
2341	rac	
2342	+	
2343	-	
2344	rac	
2345	+	
2346	-	
2347	rac	
2348	+	
2349	-	
2350	rac	
2351	+	
2652	-	
2353	rac	
2354	+	
2355	-	
2356	rac	
2357	+	
2358	-	
2359	rac	
2360	+	
2361	-	
2362	rac	
2363	+	
2364	-	
2365	rac	
2366	+	
2367	-	
2368	rac	
2369	+	
2370	-	
2371	rac	
2372	+	
2373	-	

2374	rac	
2375	+	
2376	-	
2377	rac	
2378	+	
2379	-	

160

No.	Racemic or enantiomer	R3
2380	rac	
2381	-	
2382	+	
2383	rac	
2384	+	
2385	-	
2386	rac	
2387	+	
2388	-	
2389	rac	
2390	+	
2391	-	
2392	rac	
2393	+	
2394	-	
2395	rac	
2396	+	
2397	-	
2398	rac	
2399	+	
2400	-	
2401	rac	
2402	+	
2403	-	
2404	rac	
2405	+	
2406	-	
2407	rac	
2408	+	
2409	-	
2410	rac	
2411	+	
2412	-	
2413	rac	
2414	+	
2415	-	
2416	rac	
2417	+	
2418	-	
2419	rac	
2420	+	
2421	-	

2422	rac	
2423	+	
2424	-	
2425	rac	
2426	+	
2427	-	
2428	rac	
2429	+	
2430	-	
2431	rac	
2432	+	
2433	-	
2434	rac	
2435	+	
2436	-	
2437	rac	
2438	+	
2439	-	
2440	rac	
2441	+	
2442	-	

No.	Racemic or enantiomer	Structure
2443	rac	
2444	-	
2445	+	
2446	rac	
2447	+	
2448	-	
2449	rac	
2450	+	
2451	-	
2452	rac	
2453	+	
2454	-	
2455	rac	
2456	+	
2457	-	
2458	rac	
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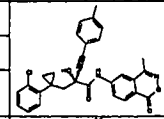
2461	rac	
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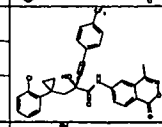
2464	rac	
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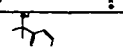
2467	rac	

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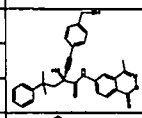
2470	rac	
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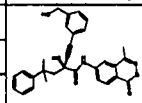
2473	rac	
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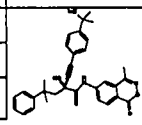
2476	rac	
2477	+	
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14. Pharmaceutical composition comprising at least one compound of the general formula I according to any of Claims 1 to 13 and, where appropriate, at least one further active ingredient together with pharmaceutically suitable excipients and/or carriers.

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

16. Pharmaceutical composition according to Claim 14, where the active ingredient may be tamoxifen, 5-(4-{5-[(RS)-(4,4,5,5,5-pentafluoropentyl)sulphinyl]pentyloxy}phenyl)-6-phenyl-8,9-dihydro-7H-benzocyclohepten-2-ol, ICI 182 780 (7alpha-[9-(4,4,5,5-pentafluoropentylsulphinyl)nonyl]estra-1,3,5(10)-triene-3,17beta-diol), 11beta-fluoro-7alpha-[5-(methyl{3-[(4,4,5,5,5-pentafluoropentyl)sulphanyl]-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, clomifen, raloxifen, fadrozole, formestane, letrozole, anastrozole or atamestane.

17. Use of compounds according to any of Claims 1 to 13 for producing a medicament.

18. Use of compounds according to Claim 17 for producing a medicament for the therapy and prophylaxis of gynaecological disorders such as endometriosis, leiomyomas of the uterus, dysfunctional bleeding and dysmenorrhoea.

19. Use of compounds according to Claim 17 for producing a medicament for the therapy and prophylaxis of hormone-dependent tumours.

20. Use of compounds according to Claim 17 for producing a medicament for the therapy and prophylaxis of breast carcinomas.

21. Use of compounds according to Claim 17 for producing a medicament for the therapy and prophylaxis of endometrial carcinoma.

22. Use of compounds according to Claim 17 for producing a medicament for the therapy and prophylaxis of ovarian carcinomas.

23. Use of compounds according to Claim 17 for producing a medicament for the therapy and prophylaxis of prostate carcinomas.

24. Use of compounds according to Claim 17 for producing a medicament for female hormone replacement therapy.

25. Use of compounds according to Claim 17 for female fertility control.

26. Process for the selective addition of lithium alkynyl and magnesium haloalkynyl compounds onto a keto amide.

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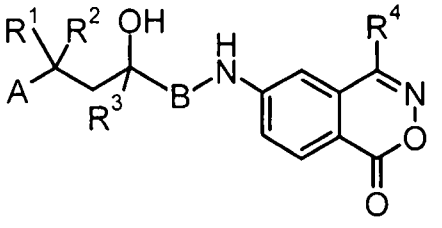
(54) Título: MODULADORES NO ESTEROIDES DE RECEPTOR DE PROGESTERONA

(57) Resumen



(I)

La presente invención se refiere a moduladores no-esteroides de receptor de progesterona de la fórmula general (I), al proceso para su preparación, al uso de los moduladores del receptor de progesterona para la producción de medicamentos 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.

MODULADORES NO ESTEROIDES DE RECEPTOR DE PROGESTERONA

MEMORIA DESCRIPTIVA

La presente invención se refiere a moduladores no esteroides de receptor de progesterona, a su uso para preparar medicamentos y a composiciones farmacéuticas que contienen estos compuestos

La hormona esteroide progesterona, regula de manera decisiva el proceso de reproducción en el organismo femenino. Durante el ciclo y en el embarazo, el ovario o la placenta segregan grandes cantidades de progesterona. Actuando conjuntamente con estrógenos, la progesterona produce modificaciones cíclicas de la mucosa del útero (endometrio) durante el ciclo menstrual. Bajo el efecto de un mayor nivel de progesterona después de la ovulación la mucosa uterina adquiere una condición que permite el nidado de un embrión (blastocito). Durante el embarazo, la progesterona controla el estado de reposo del miometrio y conserva la función del tejido decidual.

También es conocido que la progesterona inhibe la proliferación endometrial por supresión de la mitosis provocada por la acción de estrógeno en el tejido uterino (K. Chwalisz, R.M. Brenner, U. Fuhrmann, H. Hess-Stumpp, W. Elger, Steroids 65, 2000, 741-751).

También se conoce un papel significativo de la progesterona y de los receptores de progesterona en procesos patofisiológicos. Se ha comprobado la presencia de receptores de progesterona en focos de endometriosis, aunque también en tumores del útero, de mama y del sistema nervioso central. También se sabe que los leiomiomas de útero crecen según la presencia de progesterona.

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

Los moduladores de receptor de progesterona son agonistas puros o inhiben parcial o totalmente el efecto de la progesterona. Por lo tanto, las sustancias se definen como agonistas puros, agonistas parciales (SPRMS) y antagonistas puros.

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

Los antagonistas puros de receptor de progesterona inhiben completamente el efecto de la progesterona sobre el receptor de progesterona. Tienen propiedades antiovulatorias

y pueden inhibir los efectos estrógenos en el endometrio hasta la atrofia total. Por ello, son especialmente apropiados para intervenir en el proceso de reproducción femenino, p. ej. después de la ovulación, para impedir la nidación y en el embarazo, para aumentar la disposición de reacción del útero frente a prostaglandinas o oxitocina o para lograr la apertura y el ablandamiento („maduración") de la cerviz, así como para desencadenar una elevada disposición del miometrio a las contracciones.

En los focos de endometriosis o en los tejidos tumorales que están provistos de receptores de progesterona, se espera, después de la aplicación de antagonistas puros de receptor de progesterona, una acción benéfica sobre el desarrollo de la enfermedad. Podrían darse ventajas especiales para influir la evolución de enfermedades tales como endometriosis o leiomiomas de útero si se puede lograr una inhibición adicional de la ovulación por medio de los antagonistas de receptor de progesterona. Con la inhibición de la ovulación también se omite una parte de la producción hormonal del ovario y con ello, el efecto estimulador correspondiente a esta parte que desaparece sobre el tejido modificado patológicamente.

El antagonista de receptor de progesterona descrito en primer lugar, RU 486 (también mifepristona) siguió una gran cantidad de análogos de variada actividad antagonista de

receptor de progesterona. Mientras que RU 486 presenta, además del efecto antagonista de receptor de progesterona, también un efecto antiglucocorticoide, los compuestos que se sintetizaron más tarde se caracterizan, sobre todo, por un efecto más selectivo como antagonista de receptor de progesterona.

La bibliografía dio a conocer, además de compuestos esteroides como onapriston o lilopriston, que se caracterizan por una mejor disociación de efecto antagonista de receptor de progesterona/efecto anticorticoide que RU 486, también diferentes estructuras no-esteroides, cuyo efecto antagonista sobre el receptor de progesterona se está analizando [véase p. ej. 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, Volumen 23: 46-57 (2005)]. Sin embargo, los compuestos que se conocen hasta ahora poseen una actividad antagonista sólo moderada, en comparación con la de las estructuras esteroides conocidas. Los compuestos no-esteroides más efectivos se describen con actividades *in vitro* de 10 % de la actividad de RU 486.

La actividad antiglucocorticoide es desventajosa para aplicaciones terapéuticas en las cuales lo más importante de la terapia es la inhibición de los receptores de progesterona. Un efecto anticorticoide provoca efectos

secundarios no deseados con las dosificaciones requeridas por la terapia. Esto puede impedir la aplicación de una dosis apropiada para la terapia o provocar la interrupción del tratamiento.

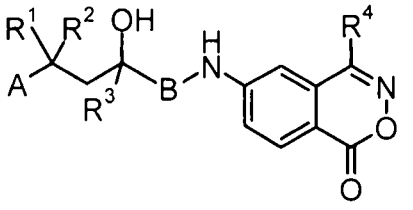
Por ello, la reducción parcial o total de las propiedades antiglucocorticoides es una condición importante para la terapia con antagonistas de receptor de progesterona, especialmente para aquellas indicaciones que requieren un tratamiento de varias semanas o meses.

Contrariamente a los antagonistas puros, los agonistas parciales de receptor de progesterona (SPRMs) presentan una propiedad agonista residual que puede ser más o menos marcada. Esto hace que estas sustancias presenten efectos agonistas potenciales en el receptor de progesterona en determinados sistemas de órganos (D. DeManno, W. Elger, R. Garg, R. Lee, b. Schneider, H. Hess-Stumpp, G. Schuber, K. Chwalisz, Steroids 68, 2003, 1019-1032). Un efecto organo-específico y disociado puede ser de utilidad terapéutica para las indicaciones descritas.

El objeto de la presente invención es, por lo tanto, ofrecer otros moduladores no-esteroides de receptor de progesterona. Estos compuestos deben poseer un efecto anticorteicoide reducido y ser apropiados, por lo tanto, para la terapia y la prevención de enfermedades ginecológicas como endometriosis, leiomiomas del útero,

sangrados disfuncionales y la dismenorrea. Además, los compuestos de la invención deben ser apropiados para la terapia y la prevención de tumores hormona-dependientes, por ejemplo, de mama, endometrio, ovario, así como carcinomas de próstata. Además, los compuestos deben ser apropiados para ser usados en el control de la fertilidad femenina y también para la terapia de sustitución hormonal en la mujer.

El objeto se logra según la presente invención, ofreciendo compuestos no-esteroides de la fórmula general I:



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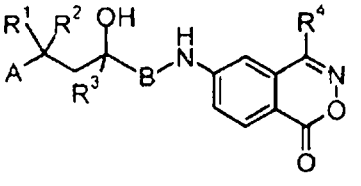


(I),

en la cual

R^1 y R^2 representan independientemente uno de otro, un átomo de hidrógeno, un grupo C_1-C_5-alquilo lineal o no-lineal, ramificado o no-ramificado, además, junto con el átomo de C de la cadena forman un anillo con un total de 3-7 miembros

R^3 representa un radical $C\equiv C-R^a$, donde

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

K significa ciano, halógeno, hidroxilo, 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 es C_3-C_{10}-cicloalquilo, heterocicloalquilo, opcionalmente mono o polisustituido con M, de manera igual o diferente o significa arilo o heteroarilo, opcionalmente mono o polisustituido con L,

L significa C_1-C_8-alquilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, C_1-C_6-perfluoralquilo, C_1-C_6-perfluoralcoxilo, C_1-C_6-alcoxi-C_1-C_6-alcoxilo, $(CH_2)_p$-C_3-C_{10}-cicloalquilo, $(CH_2)_p$-heterocicloalquilo, $(CH_2)_pCN$, $(CH_2)_pHal$, $(CH_2)_pNO_2$, $(CH_2)_p$-C_6-C_{12}-arilo, $(CH_2)_p$-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 $-(CH_2)_{n+2}-$, donde n es 1 o 2 y los átomos de oxigeno y/o carbono en posición final están unidos con átomos de carbono del anillo directamente adyacentes,

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

R^b significa un hidrógeno o un grupo C_1-C_6-alquilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, C_3-C_{10}-cicloalquilo, C_6-C_{12}-arilo o C_1-C_3-perfluoralquilo y

R^c y R^d representan independientemente uno de otro un hidrógeno, C_1-C_6-alquilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, C_3-C_{10}-cicloalquilo, C_6-C_{12}-arilo, $C(O)R^b$ o un grupo hidroxilo, donde cuando

R^c es un grupo hidroxilo, R^d solamente puede

ser un hidrógeno, un C_1-C_6-alquilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, C_3-C_{10}-cicloalquilo o C_6-C_{12}-arilo y viceversa, y

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

p puede ser un número de 0- 6,

o

R^3 representa un radical $C=C-R^gR^h$, donde

R^g y R^h representan independientemente uno de otro un hidrógeno o un C_1-C_8-alquilo, C_2-C_8-alquenilo o C_2-C_8-alquinilo, opcionalmente mono o polisustituido con X, de manera igual o diferente, donde

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

R^4 es un átomo de hidrógeno, un grupo metilo o etilo o un grupo C_1-C_3-alquilo parcial o totalmente fluorado

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

$(CH_2)_p$-heterocicloalquilo, $(CH_2)_p$CN, $(CH_2)_p$Hal, $(CH_2)_pNO_2$, $(CH_2)_p$-C_6-C_{12}-arilo, $(CH_2)_p$-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 $-(CH_2)_{n+2}-$, donde n=1 o 2 y los átomos de oxigeno y/o carbono en posición final están unidos con átomos de carbono del anillo directamente adyacentes, o

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

o

A representa un grupo alquenilo $-CR^5=CR^6R^7$, donde

R^5, R^6 y R^7 son iguales o diferentes y representan independientemente uno de otro, átomos de hidrógeno, átomos de halógeno, radicales arilo o un grupo C_1-C_5-alquilo insustituido o parcial o completamente fluorado o

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

B representa un grupo carbonilo o CH_2,

así como sus sales aceptables para uso farmacéutico.

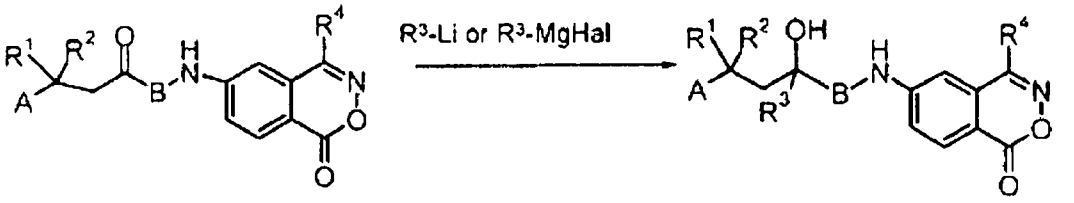
Los compuestos de la fórmula general I de la invención pueden estar presentes como estereoisómeros diferentes por la presencia de centros de asimetría. Tanto los racematos como los estereoisómeros separados forman parte del objeto de la presente invención.

La presente invención también comprende los nuevos compuestos como sustancias activas de uso farmacéutico, su preparación, su aplicación terapéutica y las formas de administración farmacéuticas que contienen las nuevas sustancias.

Los compuestos de la fórmula general (I) de la invención o sus sales aceptables para uso farmacéutico pueden usarse para preparar un medicamento, especialmente para el tratamiento y la prevención de enfermedades ginecológicas como endometriosis, leiomiomas del útero, sangrados disfuncionales y la dismenorrea. Los compuestos de la invención también se pueden usar para el tratamiento y la prevención de tumores hormona-dependientes como por ejemplo carcinoma de mama, de próstata y del endometrio.

Los compuestos de la fórmula general (I) de la invención o sus sales aceptables para uso farmacéutico son apropiados para usar en el control de la fertilidad femenina o para la terapia de sustitución hormonal en la mujer.

La presente invención se relaciona además con un proceso para preparar 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.



Los compuestos de acuerdo con la invención se preparan por adición selectiva de compuestos organometálicos a cetoamidas, por ejemplo, tal como se describió en las memorias descriptivas publicadas de WO 2002-0077356, US 6,323,199B1, 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 benzoxazinona 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 R^3. 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 un efecto fuertemente disociado en cuanto a la potencia de fijación en el receptor de progesterona y en el receptor de glucocorticoide. Mientras que los antagonistas del receptor de progesterona conocidos, tales como mifepristona (RU 486) poseen, además de la deseada elevada afinidad de fijación con el receptor de progesterona, también una elevada afinidad con el receptor de glucocorticoide, los compuestos de la invención se caracterizan por una fijación del receptor de glucocorticoide muy escasa con simultánea elevada afinidad con el receptor de progesterona.

Los sustituyentes de los compuestos de la fórmula

general I de la invención, definidos como grupos, pueden tener respectivamente las siguientes significaciones:

Se entiende por grupo C_1-C_5-, C_1-C_6- o C_1-C_8-alquilo, radicales alquilo de cadena lineal o no-lineal, ramificada o no-ramificada. Pueden ser por ejemplo: un grupo metilo, etilo, n-propilo, iso-propilo, n-, iso-, ter-butilo, un grupo n-pentilo, 2,2-dimetilpropilo, 3-metilbutilo, hexilo, heptilo u octilo.

Para R^a se prefiere el grupo metilo, etilo, n-propilo o n-butilo, así como un grupo n-pentilo.

Para R^1 y R^2 se prefiere metilo o etilo.

Se entienden por alquenilo radicales alquenilo de cadena lineal o no-lineal, ramificada o no-ramificada. En la presente invención, se entiende por grupo C_2-C_8-alquenilo, por ejemplo, los siguientes: vinilo, alilo, 3-buten-1-ilo- o 2,3-dimetil-2-propenilo. Si el sistema aromático A está sustituido con un radical C_2-C_8-alquenilo, es preferentemente un grupo vinilo.

Alquinilo hace referencia a los radicales alquinilo lineales o no-lineales, ramificados o no ramificados. Un radical C_2-C_8-alquinilo debe ser, p.ej., un grupo etinilo, propinilo, butinilo, pentinilo, hexinilo así como un grupo octinilo, preferentemente un grupo etinilo o propinilo.

Para C_3-C_{10}-cicloalquilo se menciona, por ejemplo, ciclopropilo, ciclobutilo, ciclopentilo y ciclohexilo. Se

prefiere ciclopropilo, ciclopentilo y ciclohexilo.

Se entiende por heterocicloalquilo, en el sentido de R^a, K o L, los radicales heterocicloalquilo de 3-8 miembros. Los ejemplos de heterocicloalquilo son morfolinilo,tetrahidrofuranilo, piranilo, piperazinilo, piperidinilo, pirrolidinilo, oxiranilo, oxetanilo, aziridinil, dioxolanil y dioxanilo. Aquí, la posición del heteroátomo en relación con el punto de unión puede ser cualquier posición químicamente posible.

Los posibles ejemplos del grupo C_1-C_6-alcoxil-C_1-C_6-alcoxilo son metoximetoxilo, etoximetoxilo o 2-metoxietoxilo.

En esta invención, un radical OR^b es un grupo hidroxilo, metoxilo, etoxilo, n-propoxilo, iso-propoxilo, n-, iso-, ter-butoxilo o n-pentoxilo, 2,2-dimetilpropoxilo o 3-metilbutoxilo. Se prefieren hidroxilo, metoxilo y etoxilo.

Para un grupo C_1-C_5-alquilo parcial o totalmente fluorado son adecuados los grupos alquilo perfluorados que se mencionan más arriba. De estos se prefieren en particular, el grupo trifluorometilo o pentafluoretilo, y los grupos alquilo parcialmente fluorados, p.ej., el grupo 5,5,4,4-pentafluoropentilo o 5,5,5,4,4,3,3-heptafluoropentilo.

Un átomo de halógeno puede estar representado por un átomo de flúor, cloro, bromo o yodo. 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, este es por ejemplo, un anillo ciclopropilo, -butilo, -pentilo o -hexilo. Se prefiere el anillo ciclopropilo o ciclopentilo.

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

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

Como radical heterocíclico se puede utilizar, p.ej. 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, en particular, todos los isómeros posibles en cuanto a las posiciones de los heteroátomos.

R^3 hace referencia cuando se trata de un radical arilo, un radical fenilo, 1- o 2-naftilo, opcionalmente sustituido; se prefiere el radical fenilo. Los 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.

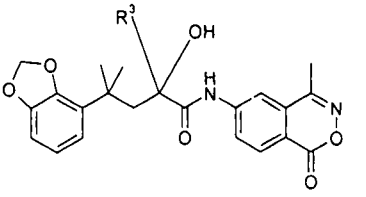
El número p para un radical $(CH_2)_p$ puede ser un número de 0 a 6, preferentemente de 0 a 2. De acuerdo con la invención, "radical" hace referencia a todos los grupos funcionales que se mencionan en combinación con $(CH_2)_p$.

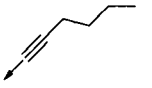
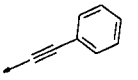
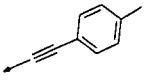
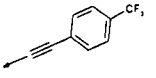
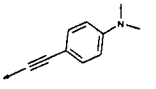
En el caso donde los compuestos de la fórmula general I (B = $-CH_2-$) se encuentren bajo la forma de sales, pueden ser en forma de clorhidrato, sulfato, nitrato, tartrato, citrato, fumarato, succinato o benzoato.

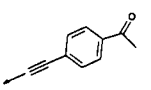
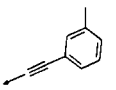
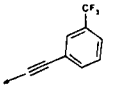
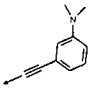
Si los compuestos de acuerdo con la invención se encuentran presentes en forma de mezclas racémicas, se pueden separar de acuerdo con métodos de separación de racematos conocidos por los especialistas en la técnica, para obtener las formas puras, óptimamente activas. Por ejemplo, las mezclas racémicas se pueden separar por cromatografía con un vehículo que a su vez es ópticamente activo (CHIRALPAK AD®) para obtener los isómeros puros. También es posible esterificar el grupo hidroxilo libre de un compuesto racémico de la fórmula general I con un ácido ópticamente activo y separar los ésteres diastereoisómeros por cristalización fraccionada o cromatografía y saponifar los ésteres separados para obtener los respectivos isómeros ópticamente puros. Como ácidos ópticamente activos se pueden utilizar, por ejemplo, ácido mandélico, ácido alcanforsulfónico o ácido tartárico.

Según la invención se prefieren los compuestos que se

mencionan a continuación y su uso:



°	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	
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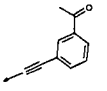
33	-	
34	Rac	
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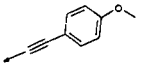
36	-	
37	Rac	
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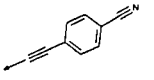
39	-	
40	Rac	
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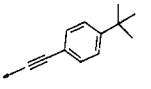
42	-	
43	Rac	
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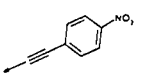
45	-	

46	Rac	
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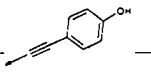
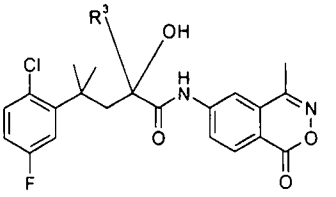
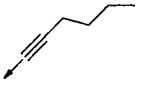
48	-	
49	Rac	
50	+	
51	-	



N°	Racémico o enantiómero	R3
52	rac	
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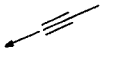
54	+	
55	rac	
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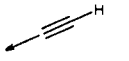
58	rac	
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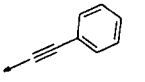
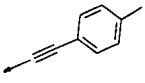
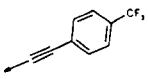
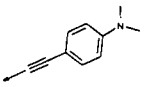
61	rac	
62	+	
63	-	
64	rac	
65	+	
66	-	
67	rac	

68	+	
69	-	
70	rac	
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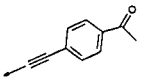
72	-	
73	rac	
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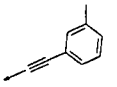
75	-	
76	rac	
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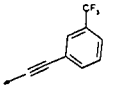
78	-	
79	rac	
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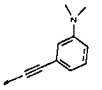
81	-	
82	rac	
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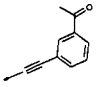
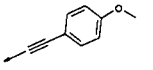
84	-	
85	rac	
86	+	
87	-	
88	rac	
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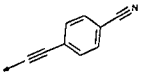
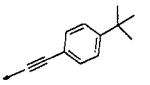
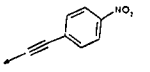
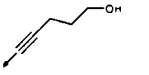
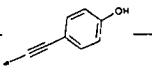
90	-	
91	rac	

92	+	
93	-	
94	rac	
95	+	
96	-	
97	rac	
98	+	
99	-	
100	rac	
191	+	
102	-	
103	rac	
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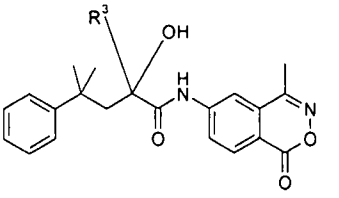
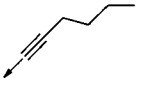
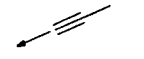
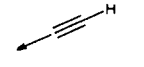
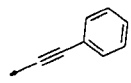
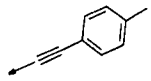
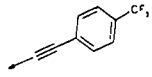
105	-	



N°	Racémico o enantiómero	R3
106	rac	
107	-	
108	+	
109	rac	
110	+	
111	-	
112	rac	
113	+	

114	-	
115	Rac	
116	+	
117	-	
118	Rac	
119	+	
120	-	
121	Rac	
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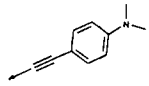
123	-	
124	Rac	
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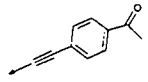
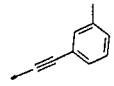
127	Rac	
128	+	
129	-	
130	Rac	
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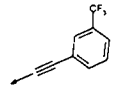
133	Rac	
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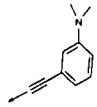
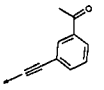
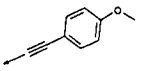
135	-	
136	Rac	
137	+	

138	-	
139	rac	
140	+	
141	-	
142	rac	
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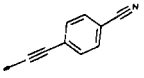
144	-	
145	rac	
146	+	
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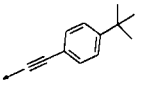
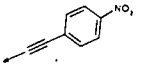
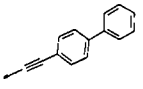
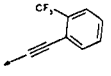
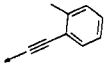
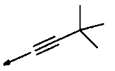
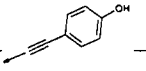
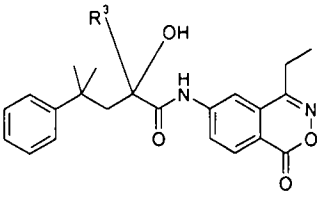
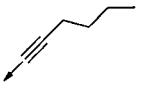
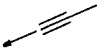
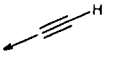
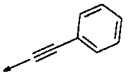
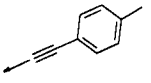
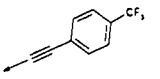
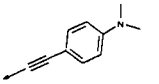
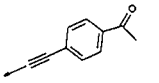
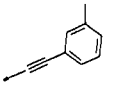
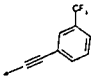
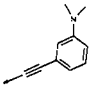
148	rac	
149	+	
150	-	
151	rac	
152	+	
153	-	
154	rac	
155	+	
156	-	
157	rac	
158	+	
159	-	
160	rac	
161	+	

162	-	
163	Rac	
164	+	
165	-	
166	Rac	
167	+	
168	-	



N°	Racémico o enantiómero	R3
169	rac	
170	-	
171	+	
172	rac	
173	+	
174	-	
175	rac	
176	+	
177	-	
178	rac	
179	+	
180	-	
181	rac	
182	+	

190

183	-	
184	rac	
185	+	
186	-	
187	rac	
188	+	
189	-	
190	rac	
191	+	
192	-	
193	rac	
194	+	
195	-	
196	rac	
197	+	
198	-	
199	rac	
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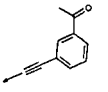
201	-	
202	rac	
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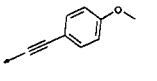
205	rac	
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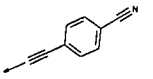
208	rac	
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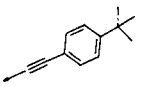
211	rac	
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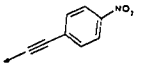
214	rac	
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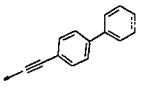
217	rac	
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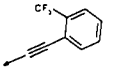
220	rac	
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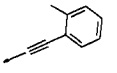
223	rac	
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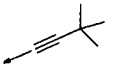
226	rac	
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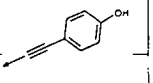
229	rac	
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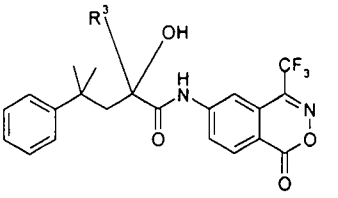
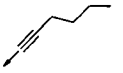


N°	Racémico o enantiómero	R3
232	rac	
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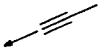
235	rac	
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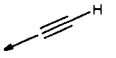
238	rac	
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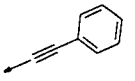
241	rac	
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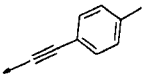
244	rac	
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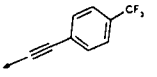
247	rac	
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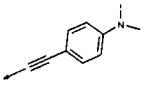
250	rac	
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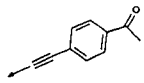
252	-	

253	rac	
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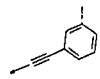
256	rac	
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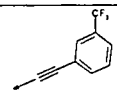
259	rac	
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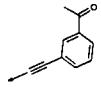
265	rac	
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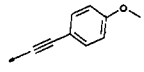
268	rac	
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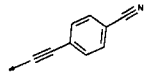
271	rac	
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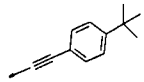
274	rac	
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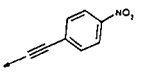
277	rac	
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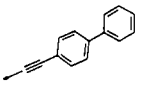
280	rac	
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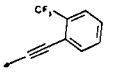
283	rac	
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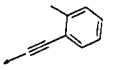
286	rac	
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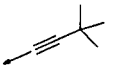
289	rac	
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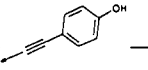
292	rac	
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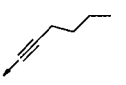
294	-	

N°	Racémico o enantiómero	R3
295	rac	
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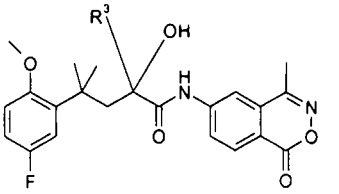
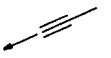
297	+	



298	rac	
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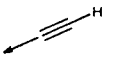
301	rac	
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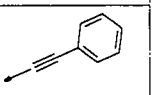
304	rac	
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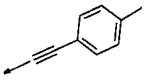
307	rac	
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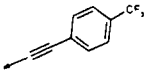
310	rac	
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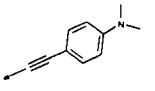
313	rac	
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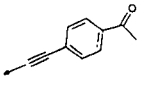
316	rac	
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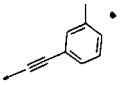
319	rac	
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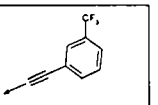
322	rac	
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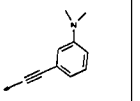
325	rac	
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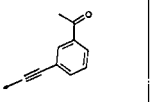
328	rac	
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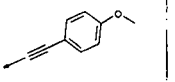
331	rac	
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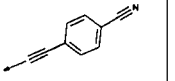
334	rac	
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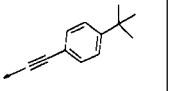
337	rac	
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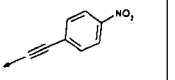
339	-	
340	rac	
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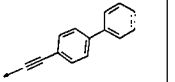
343	rac	
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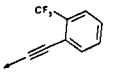
346	rac	
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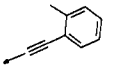
349	rac	
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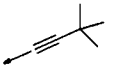
352	rac	
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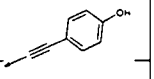
355	rac	
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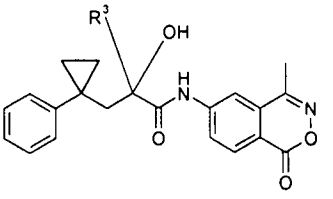
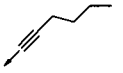
357	-	



N°	Racémico o enantiómero	R3
358	rac	
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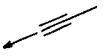
361	rac	
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363	-	
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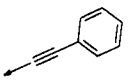
365	+	
366	-	

367	rac	
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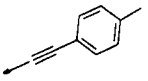
370	rac	
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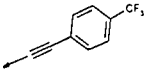
372	-	
373	rac	
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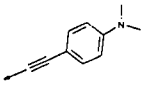
376	rac	
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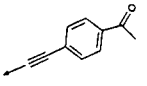
378	-	
379	rac	
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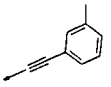
382	rac	
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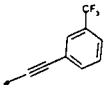
384	-	
385	rac	
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387	-	
388	rac	
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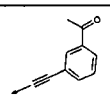
390	-	

391	rac	
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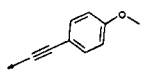
393	-	
394	rac	
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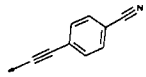
396	-	
397	rac	
398	+	
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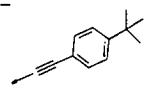
400	rac	
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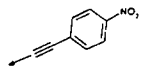
403	rac	
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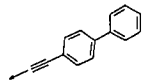
406	rac	
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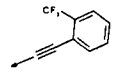
408	-	
409	rac	
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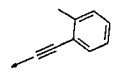
412	rac	
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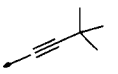
415	rac	
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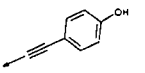
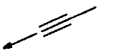
418	rac	
419	+	
420	-	

N°	Racémico o enantiómero	R3
421	rac	
422	-	
423	+	
424	rac	
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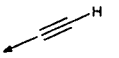
427	rac	
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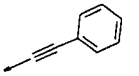
430	rac	
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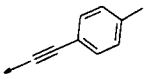
433	rac	
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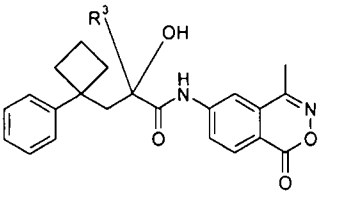
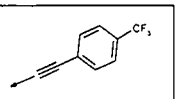
435	-	



436	rac	
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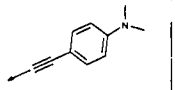
438	-	
439	rac	
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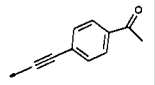
442	rac	
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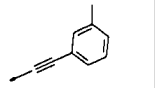
445	rac	
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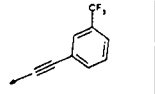
448	rac	
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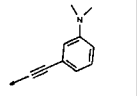
451	rac	
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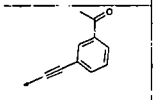
454	rac	
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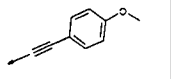
457	rac	
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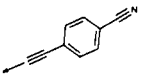
460	rac	
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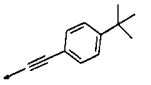
463	rac	
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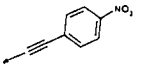
466	rac	
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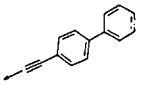
469	rac	
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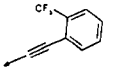
472	rac	
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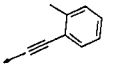
475	rac	
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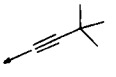
478	rac	
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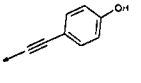
481	rac	
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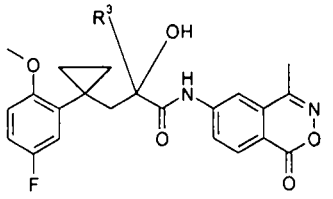
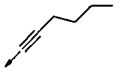
483	-	



N°	Racémico o enantiómero	R3
484	rac	
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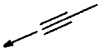
487	rac	
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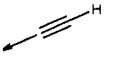
490	rac	
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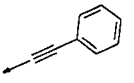
493	rac	
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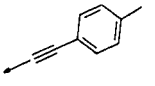
496	rac	
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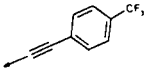
499	rac	
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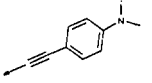
502	rac	
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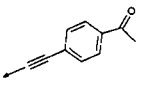
505	rac	

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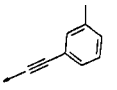
508	rac	
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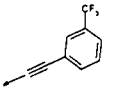
511	rac	
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518	+	
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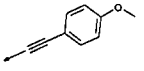
520	rac	
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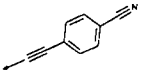
523	rac	
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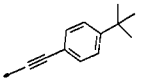
526	rac	
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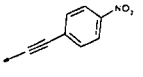
529	rac	
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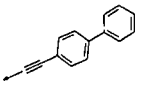
532	rac	
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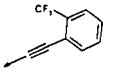
535	rac	
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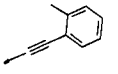
538	rac	
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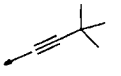
541	rac	
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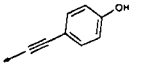
544	rac	
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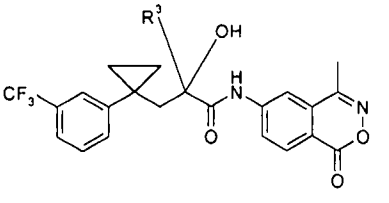
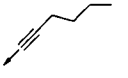


N°	Racémico o enantiómero	R3
547	rac	
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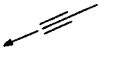
550	rac	
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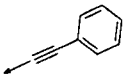
556	rac	
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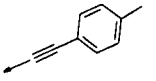
559	rac	
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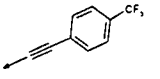
562	rac	
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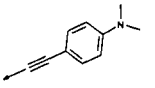
565	rac	
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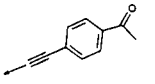
568	rac	
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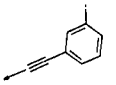
571	rac	
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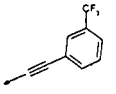
574	rac	
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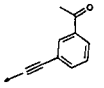
580	rac	
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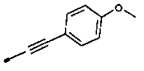
583	rac	
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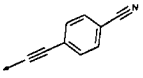
586	rac	
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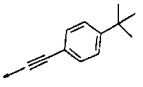
589	rac	
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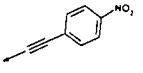
592	rac	
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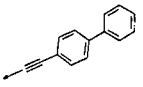
595	rac	
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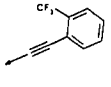
598	rac	
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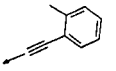
601	rac	
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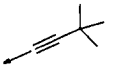
604	rac	
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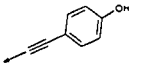
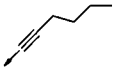
607	rac	
608	+	
609	-	

N°	Racémico o enantiómero	R3
610	rac	
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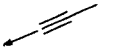
613	rac	
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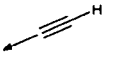
616	rac	
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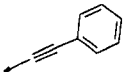
619	rac	
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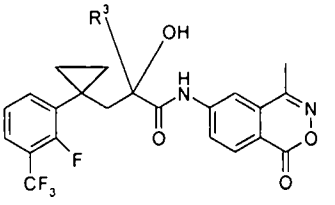

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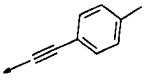
622	rac	
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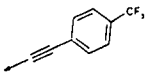
625	rac	
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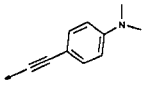
627	-	
628	rac	
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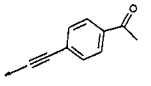
630	-	
631	rac	
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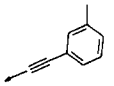
634	rac	
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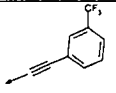
637	rac	
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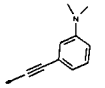
640	rac	
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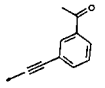
643	rac	
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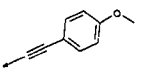
646	rac	
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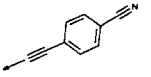
649	rac	
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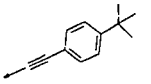
652	rac	
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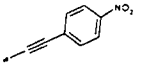
655	rac	
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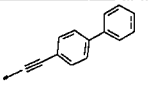
658	rac	
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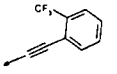
661	rac	
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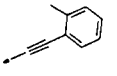
664	rac	
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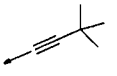
667	rac	
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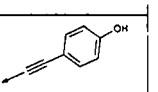
669	-	
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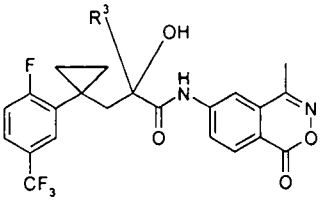
672	-	



N°	Racémico o enantiómero	R3
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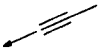
674	-	
675	+	
676	rac	
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678	-	
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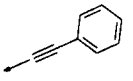
680	+	
681	-	
682	rac	
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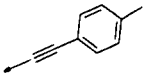
684	-	
685	rac	
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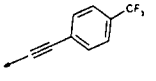
687	-	
688	rac	
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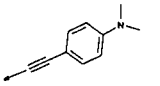
691	rac	
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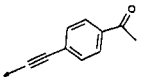
694	rac	
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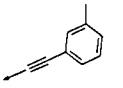
697	rac	
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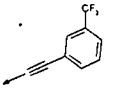
700	rac	
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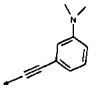
703	rac	
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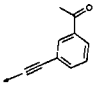
706	rac	
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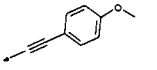
709	rac	
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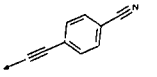
712	rac	
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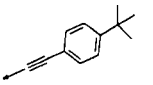
714	-	

715	Rac	
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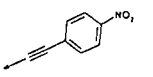
717	-	
718	Rac	
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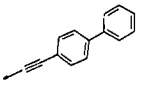
721	Rac	
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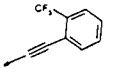
723	-	
724	Rac	
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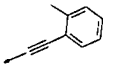
726	-	
727	rac	
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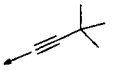
730	rac	
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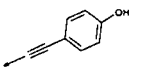
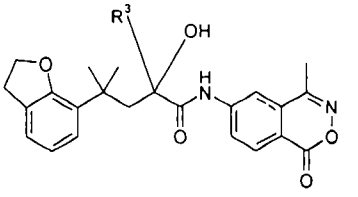
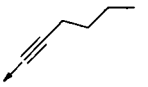
733	rac	
734	+	
735	-	

N°	Racémico o enantiómero	R3



736	rac	
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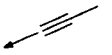
739	rac	
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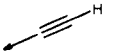
742	rac	
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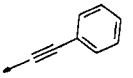
745	rac	
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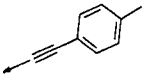
748	rac	
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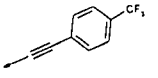
751	rac	
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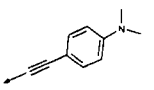
753	-	
754	rac	
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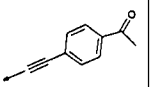
756	-	
757	rac	
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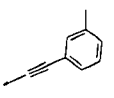
759	-	
760	rac	

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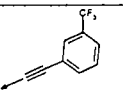
763	rac	
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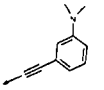
766	rac	
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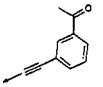
768	-	
769	rac	
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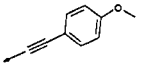
772	rac	
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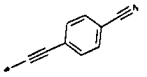
775	rac	
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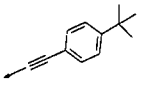
778	rac	
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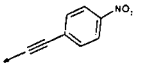
781	rac	
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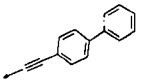
784	rac	
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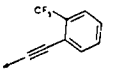
787	rac	
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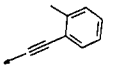
790	rac	
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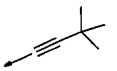
793	rac	
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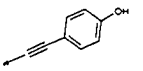
796	rac	
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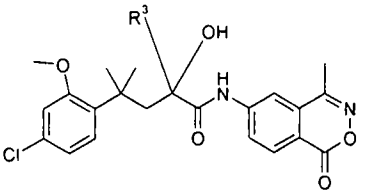
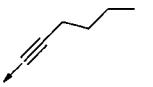


N°	Racémico o enantiómero	R3
799	rac	
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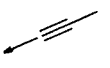
801	+	
802	rac	
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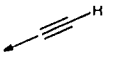
805	rac	
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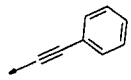
807	-	
808	rac	
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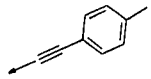
811	rac	
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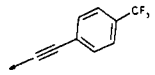
814	rac	
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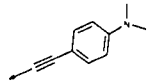
817	rac	
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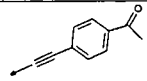
819	-	
820	rac	
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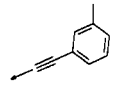
823	rac	
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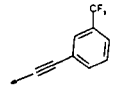
825	-	
826	rac	
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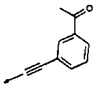
831	-	

832	rac	
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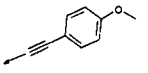
835	rac	
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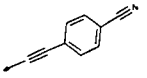
838	rac	
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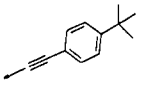
841	rac	
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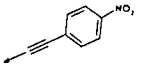
844	rac	
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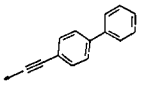
847	rac	
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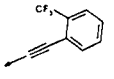
849	-	
850	Rac	
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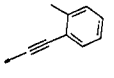
853	rac	
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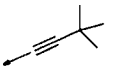
856	rac	
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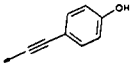
858	-	
859	rac	
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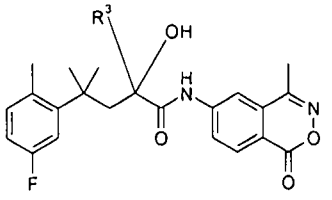
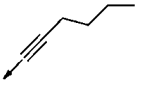
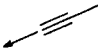


N°	Racémico o enantiómero	R3
862	rac	
863	-	
864	+	
865	rac	
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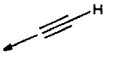
868	rac	
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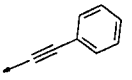
871	rac	
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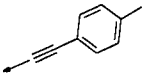
874	rac	
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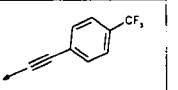
877	rac	
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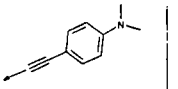
880	rac	
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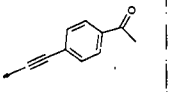
882	-	
883	rac	
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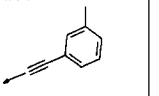
885	-	
886	rac	
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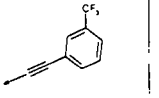
888	-	
889	rac	
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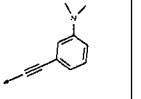
892	rac	
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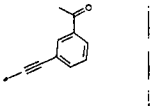
895	rac	
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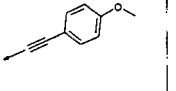
898	rac	
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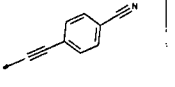
901	rac	

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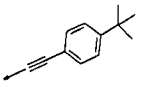
904	rac	
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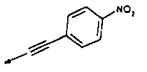
906	-	
907	rac	
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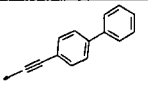
910	rac	
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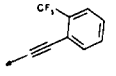
913	rac	
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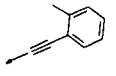
916	rac	
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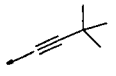
919	rac	
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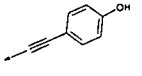
922	rac	
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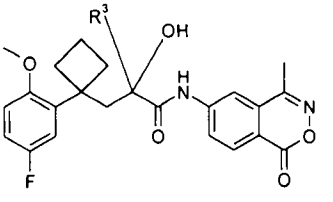
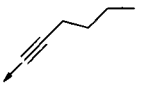


230

N°	Racémico o enantiómero	R3
925	rac	
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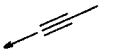
928	rac	
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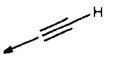
931	rac	
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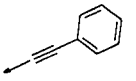
934	rac	
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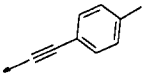
937	rac	
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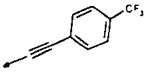
940	rac	
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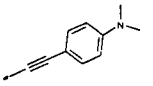
942	-	
943	rac	
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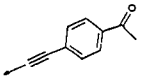
945	-	
946	rac	
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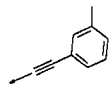
949	rac	
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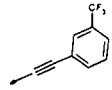
952	rac	
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954	-	
955	rac	
956	+	
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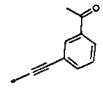
958	rac	
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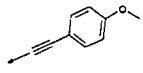
961	rac	
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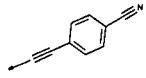
964	rac	
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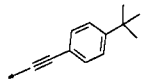
967	rac	
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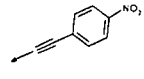
970	rac	
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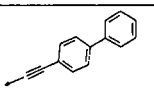
973	rac	
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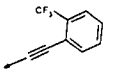
976	rac	
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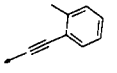
979	rac	
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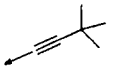
982	rac	
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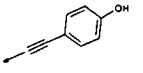
985	rac	
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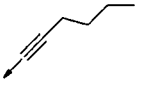
987	-	

N°	Racémico o enantiómero	R3
988	rac	
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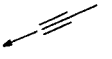
991	rac	
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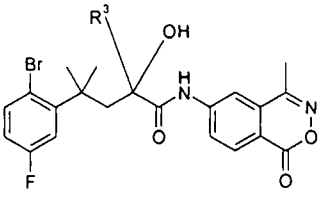

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994	rac	
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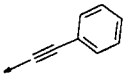
996	-	
997	rac	
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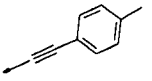
1000	rac	
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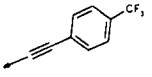
1003	rac	
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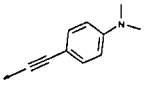
1006	rac	
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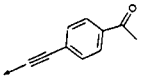
1009	rac	
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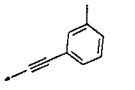
1012	rac	
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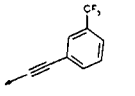
1015	rac	
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1017	-	

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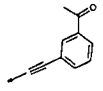
1021	rac	
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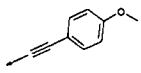
1024	rac	
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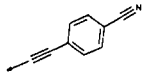
1027	rac	
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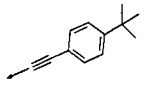
1030	rac	
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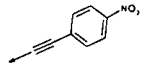
1033	rac	
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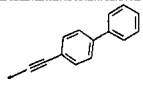
1035	-	
1036	rac	
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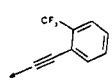
1038	-	
1039	rac	
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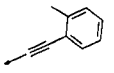
1042	rac	
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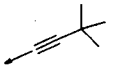
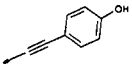
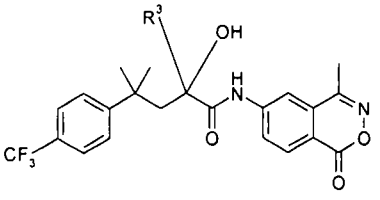
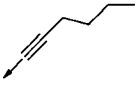
1045	rac	
1046	+	
1047	-	
1048	rac	
1049	+	
1050	-	



N°	Racémico o enantiómero	R3
1051	rac	
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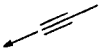
1053	+	
1054	rac	
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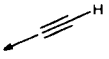
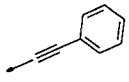
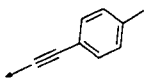
1056	-	
1057	rac	
1058	+	
1059	-	
1060	rac	
1061	+	
1062	-	

1063	rac	
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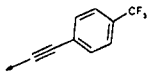
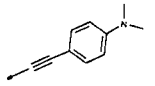
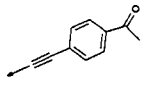
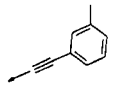
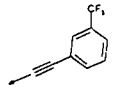
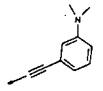
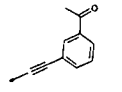
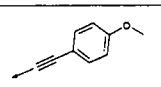
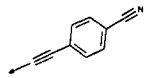
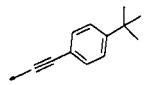
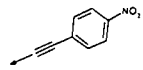
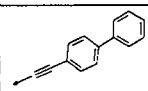
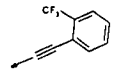
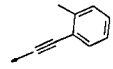
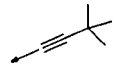
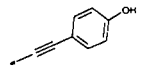
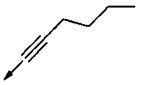
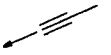
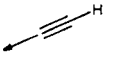
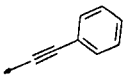
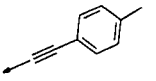
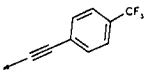
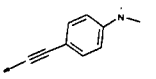
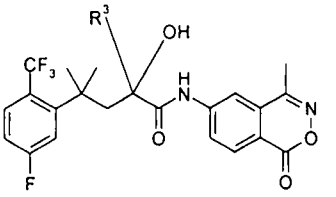
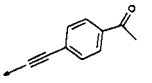
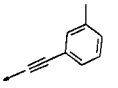
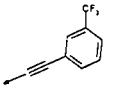
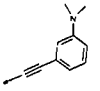
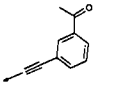
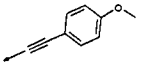
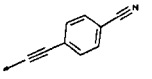
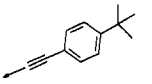
1066	rac	
1067	+	
1068	-	
1069	rac	
1070	+	
1071	-	
1072	rac	
1073	+	
1074	-	
1075	rac	
1076	+	
1077	-	
1078	rac	
1079	+	
1080	-	
1081	rac	
1082	+	
1083	-	
1084	rac	
1085	+	
1086	-	
1087	rac	

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	

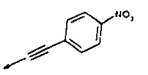
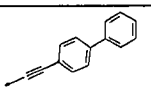
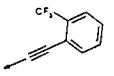
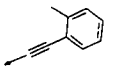
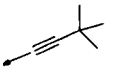
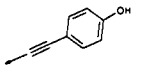
1112	+
1113	-

N°	Racémico o enantiómero	R3
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	+	

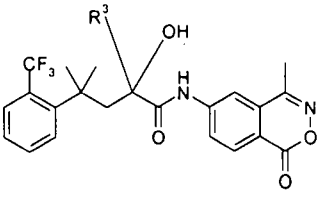


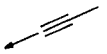
1134	-	
1135	rac	
1136	+	
1137	-	
1138	rac	
1139	+	
1140	-	
1141	rac	
1142	+	
1143	-	
1144	rac	
1145	+	
1146	-	
1147	rac	
1148	+	
1149	-	
1150	rac	
1151	+	
1152	-	
1153	rac	
1154	+	
1155	-	
1156	rac	
1157	+	

240

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	-	

N°	Racémico o enantiómero	R3
1177	rac	
1178	-	



1179	+	
1180	rac	
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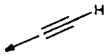
1183	rac	
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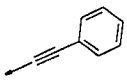
1186	rac	
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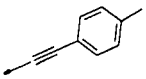
1189	rac	
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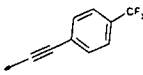
1192	rac	
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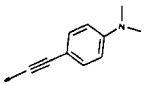
1195	rac	
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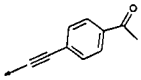
1198	rac	
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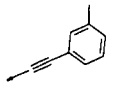
1202	rac	
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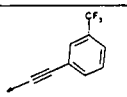
1204	rac	
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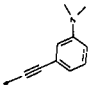
1207	rac	
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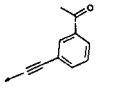
1210	rac	
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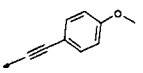
1213	rac	
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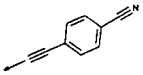
1216	rac	
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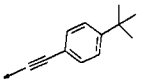
1219	rac	
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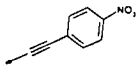
1222	rac	
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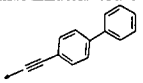
1225	rac	
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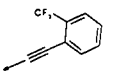
1227	-	
1228	rac	
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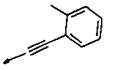
1231	rac	
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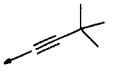
1234	rac	
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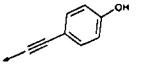
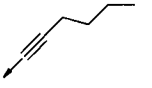
1237	rac	
1238	+	
1239	-	

N°	Racémico o enantiómero	R3
1240	rac	
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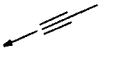
1243	rac	
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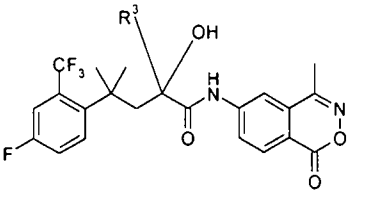
1247	+	



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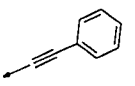
1249	rac	
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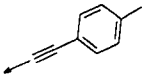
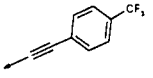
1251	-	
1252	rac	
1253	+	
1254	-	
1255	rac	
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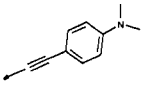
1257	-	
1258	rac	
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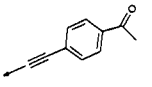
1260	-	
1261	rac	
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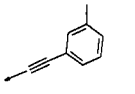
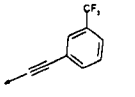
1263	-	
1264	rac	
1265	+	
1266	-	
1267	rac	
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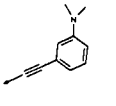
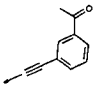
1269	-	
1270	rac	
1271	+	

1272	-	
1273	rac	
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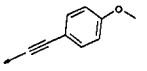
1275	-	
1276	rac	
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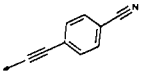
1278	-	
1279	rac	
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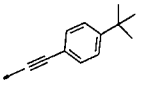
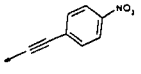
1281	-	
1282	rac	
1283	+	
1284	-	
1285	rac	
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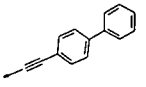
1287	-	
1288	rac	
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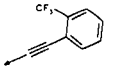
1291	rac	
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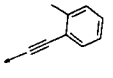
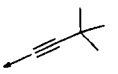
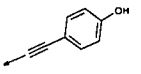
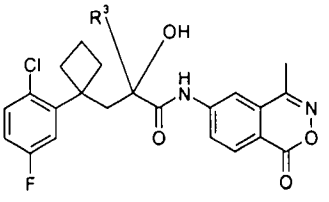
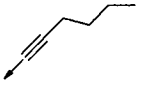
1293	-	
1294	rac	
1295	+	

1296	-	
1297	rac	
1298	+	
1299	-	
1300	rac	
1301	+	
1302	-	



N°	Racémico o enantiómero	R3
1303	rac	
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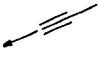
1306	rac	
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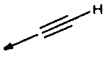
1309	rac	
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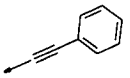
1311	-	
1312	rac	
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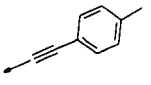
1314	-	
1315	rac	

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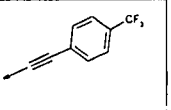
1318	rac	
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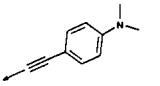
1321	rac	
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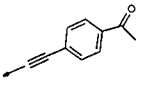
1324	rac	
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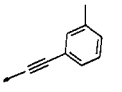
1327	rac	
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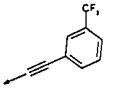
1330	rac	
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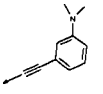
1333	rac	
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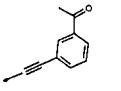
1336	rac	
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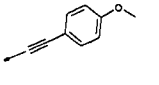
1339	rac	
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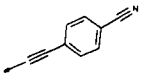
1342	rac	
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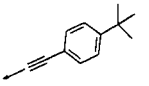
1345	rac	
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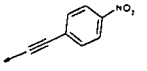
1348	rac	
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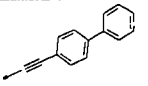
1351	rac	
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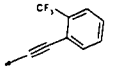
1354	rac	
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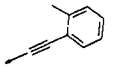
1357	rac	
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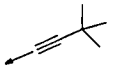
1360	rac	
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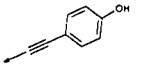
1362	rac	
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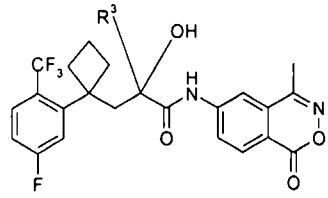
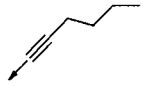
1365	-	



N°	Racémico o enantiómero	R3
1366	rac	
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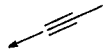
1368	+	
1369	rac	
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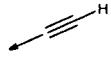
1371	-	
1372	rac	
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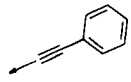
1375	rac	
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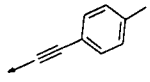
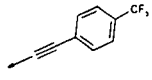
1377	-	
1378	rac	
1379	+	
1380	-	
1381	rac	
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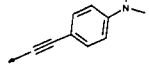
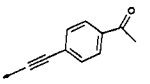
1384	rac	
1385	+	
1386	-	

250

1387	rac	
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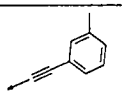
1389	-	
1390	rac	
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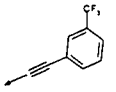
1393	rac	
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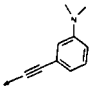
1396	rac	
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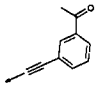
1398	-	
1399	rac	
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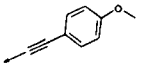
1401	-	
1402	rac	
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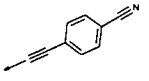
1404	-	
1405	rac	
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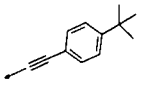
1407	-	
1408	rac	
1409	+	
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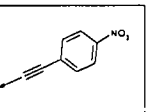
1411	rac	
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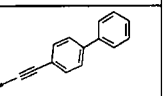
1414	rac	
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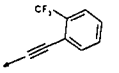
1417	rac	
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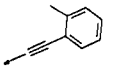
1420	rac	
1421	+	
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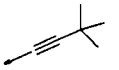
1423	rac	
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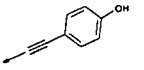
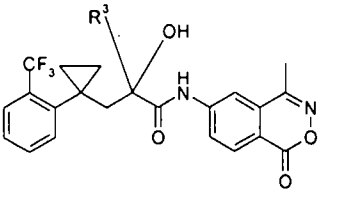
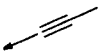
1426	rac	
1427	+	
1428	-	

N°	Racémico o enantiómero	R3
1429	rac	
1430	-	
1431	+	



1432	rac	
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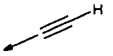
1434	-	
1435	rac	
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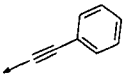
1437	-	
1438	rac	
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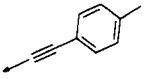
1440	-	
1441	rac	
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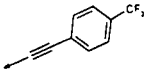
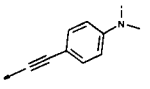
1443	-	
1444	rac	
1445	+	
1446	-	
1447	rac	
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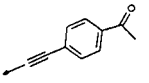
1450	rac	
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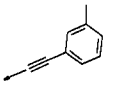
1452	-	
1453	rac	
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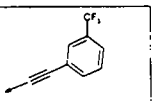
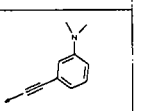
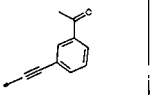
1455	-	

1456	rac	
1457	+	
1458	-	
1459	rac	
1460	+	
1461	-	
1462	rac	
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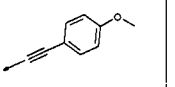
1465	rac	
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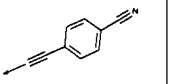
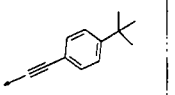
1468	rac	
1469	+	
1470	-	
1471	rac	
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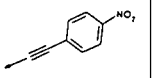
1473	-	
1474	rac	
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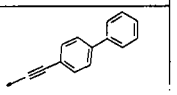
1477	rac	
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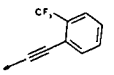
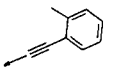
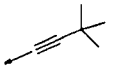
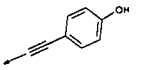
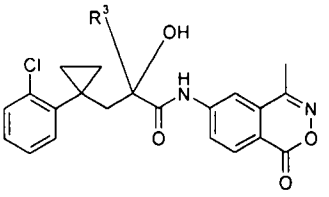
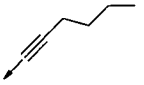
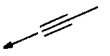
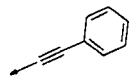
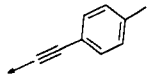
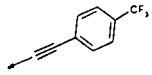
1479	-	

1480	rac	
1481	+	
1482	-	
1483	rac	
1484	+	
1485	-	
1486	rac	
1487	+	
1488	-	
1489	rac	
1490	+	
1491	-	



N°	Racémico o enantiómero	R3
1492	rac	
1493	-	
1494	+	
1495	rac	
1496	+	
1497	-	
1498	rac	
1499	+	
1500	-	

1501	rac	
1502	+	
1503	-	
1504	rac	
1505	+	
1506	-	
1507	rac	
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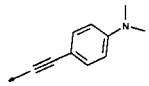
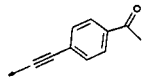
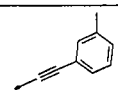
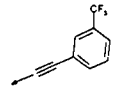
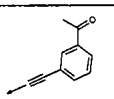
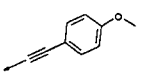
1509	-	
1510	rac	
1511	+	
1512	-	
1513	rac	
1514	+	
1515	-	
1516	rac	
1517	+	
1518	-	
1519	rac	
1520	+	
1521	-	
1522	rac	
1523	+	
1524	-	

1525	rac	
1526	+	
1527	-	
1528	rac	
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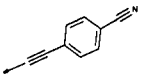
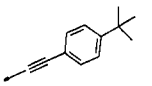
1531	rac	
1532	+	
1533	-	
1534	rac	
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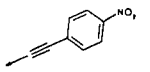
1536	-	
1537	rac	
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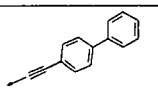
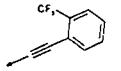
1539	-	
1540	rac	
1541	+	
1542	-	
1543	rac	
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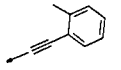
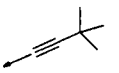
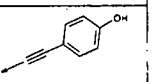
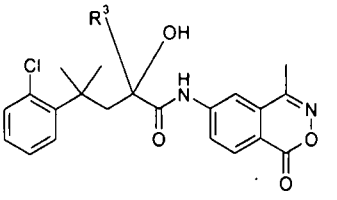
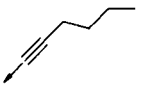
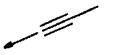
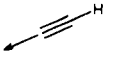
1545	-	
1546	rac	
1547	+	
1548	-	

1549	rac	
1550	+	
1551	-	
1552	rac	
1553	+	
1554	-	



N°	Racémico o enantiómero	R3
1555	rac	
1556	-	
1557	+	
1558	rac	
1559	+	
1560	-	
1561	rac	
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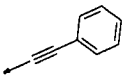
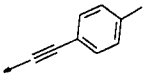
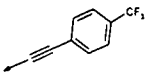
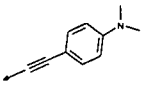
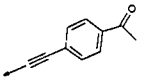
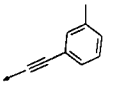
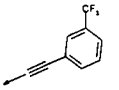
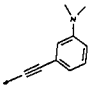
1563	-	
1564	rac	
1565	+	
1566	-	
1567	rac	
1568	+	
1569	-	

1570	rac	
1571	+	
1572	-	
1573	rac	
1574	+	
1575	-	
1576	rac	
1577	+	
1578	-	
1579	rac	
1580	+	
1581	-	
1582	rac	
1583	+	
1584	-	
1585	rac	
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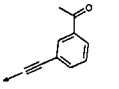
1588	rac	
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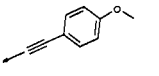
1591	rac	
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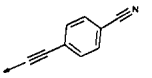
1594	rac	
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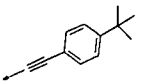
1597	rac	
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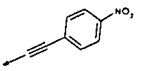
1600	rac	
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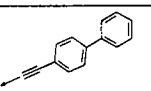
1603	rac	
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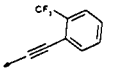
1606	rac	
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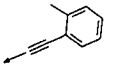
1608	-	
1609	rac	
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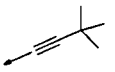
1612	rac	
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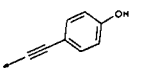
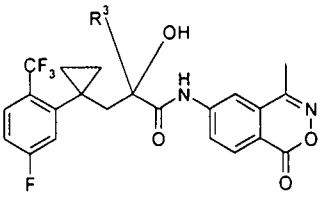
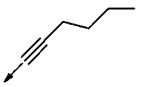
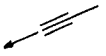
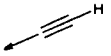
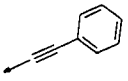
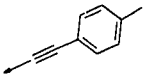
1614	-	
1615	rac	
1616	+	
1617	-	

260



N°	Racémico o enantiómero	R3
1618	rac	
1619	-	
1620	+	
1621	rac	
1622	+	
1623	-	
1624	rac	
1625	+	
1626	-	
1627	rac	
1628	+	
1629	-	
1630	rac	
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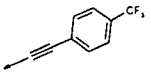
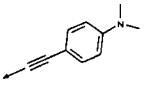
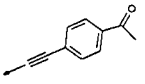
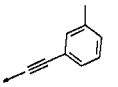
1632	-	
1633	rac	
1634	+	
1635	-	
1636	rac	
1637	+	
1638	-	
1639	rac	
1640	+	

1641	-	
1642	rac	
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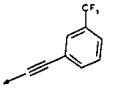
1645	rac	
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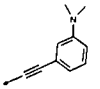
1647	-	
1648	rac	
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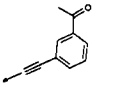
1650	-	
1651	rac	
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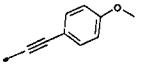
1653	-	
1654	rac	
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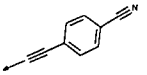
1656	-	
1657	rac	
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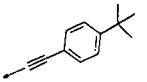
1660	rac	
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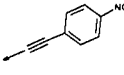
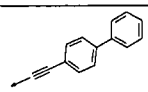
1662	-	
1663	rac	
1664	+	

1665	-	
1666	rac	
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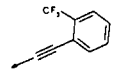
1668	-	
1669	rac	
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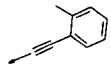
1672	rac	
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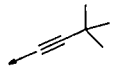
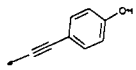
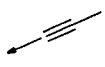
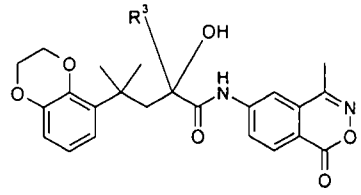
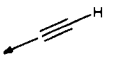
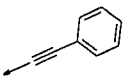
1674	-	
1675	rac	
1676	+	
1677	-	
1678	rac	
1679	+	
1680	-	

N°	Racémico o enantiómero	R3
1681	rac	
1682	-	
1683	+	
1684	rac	
1685	+	



1686	-	
1687	rac	
1688	+	
1689	-	
1690	rac	
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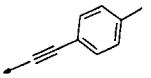
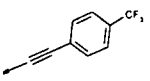
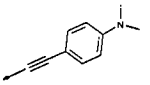
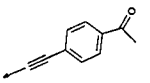
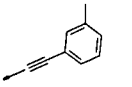
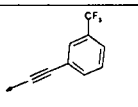
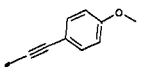
1692	-	
1693	rac	
1694	+	
1695	-	
1696	rac	
1697	+	
1698	-	
1699	rac	
1700	+	
1701	-	
1702	rac	
1703	+	
1704	-	
1705	rac	
1706	+	
1707	-	
1708	rac	
1709	+	

1710	-	
1711	rac	
1712	+	
1713	-	
1714	rac	
1715	+	
1716	-	
1717	rac	
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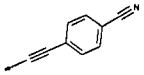
1719	-	
1720	rac	
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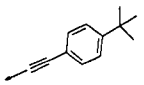
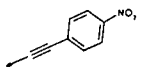
1722	-	
1723	rac	
1724	+	
1725	-	
1726	rac	
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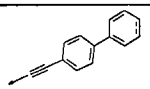
1728	-	
1729	rac	
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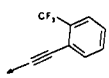
1731	-	
1732	rac	
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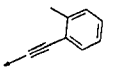
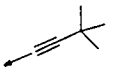
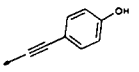
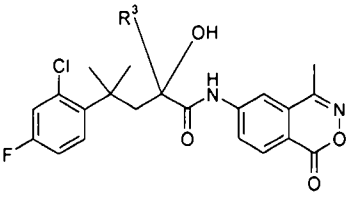
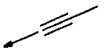
1734	-	
1735	rac	
1736	+	
1737	-	
1738	rac	
1739	+	
1740	-	
1741	rac	
1742	+	
1743	-	



N°	Racémico o enantiómero	R3
1744	rac	
1745	-	
1746	+	
1747	rac	
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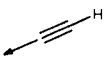
1750	rac	
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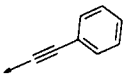
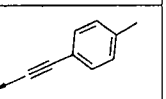
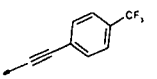
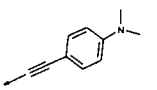
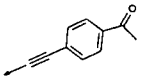
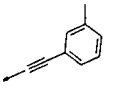
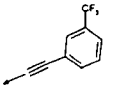
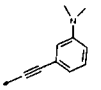
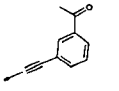
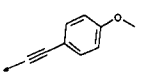
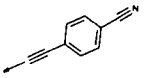
1753	rac	

1754	+	
1755	-	
1756	rac	
1757	+	
1758	-	
1759	rac	
1760	+	
1761	-	
1762	rac	
1763	+	
1764	-	
1765	rac	
1766	+	
1767	-	
1768	rac	
1769	+	
1770	-	
1771	rac	
1772	+	
1773	-	
1774	rac	
1775	+	
1776	-	
1777	rac	
1778	+	

1779	-	
1780	rac	
1781	+	
1782	-	
1783	rac	
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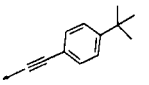
1786	rac	
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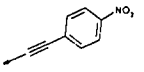
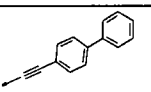
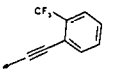
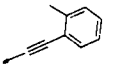
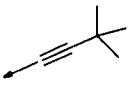
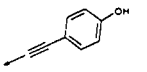
1789	rac	
1790	+	
1791	-	
1792	rac	
1793	+	
1794	-	
1795	rac	
1796	+	
1797	-	
1798	rac	
1799	+	
1800	-	
1801	rac	
1802	+	

1803	-	
1804	rac	
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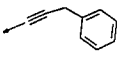
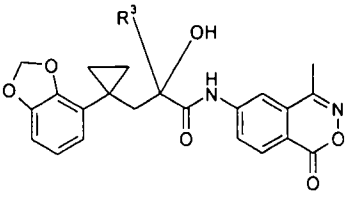
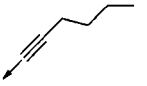
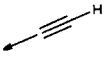
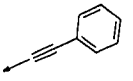
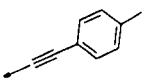
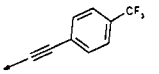
1806	-	
1807	rac	
1808	+	
1809	-	
1810	rac	
1811	+	
1812	-	



N°	Racémico o enantiómero	R3
1813	rac	
1814	-	
1815	+	
1816	rac	
1817	+	
1818	-	
1819	rac	
1820	+	
1821	-	
1822	rac	
1823	+	

1824	-	
1825	rac	
1826	+	
1827	-	
1828	rac	
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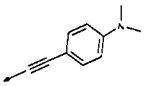
1831	rac	
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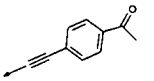
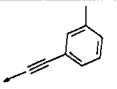
1833	-	
1834	rac	
1835	+	
1836	-	
1837	rac	
1838	+	
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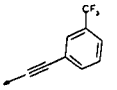
1840	rac	
1841	+	
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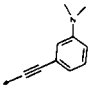
1843	rac	
1844	+	
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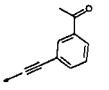
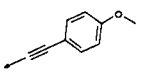
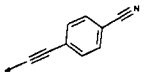
1846	rac	
1847	+	

1848	-	
1849	rac	
1850	+	
1851	-	
1852	rac	
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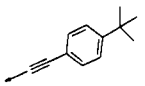
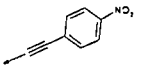
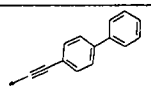
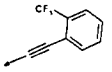
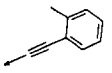
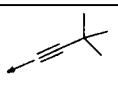
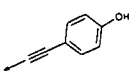
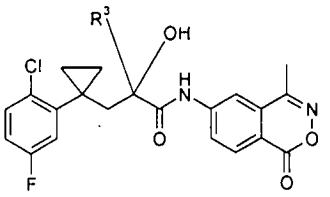
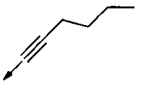
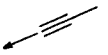
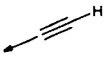
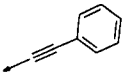
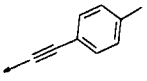
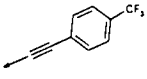
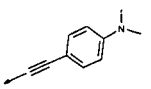
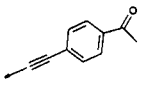
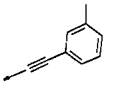
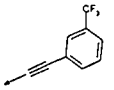
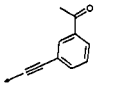
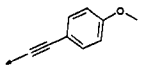
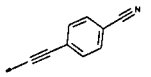
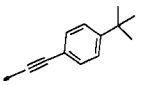
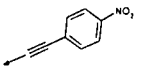
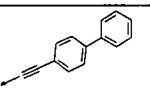
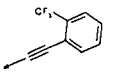
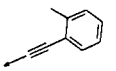
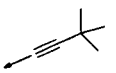
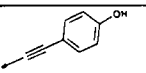
1854	-	
1855	rac	
1856	+	
1857	-	
1858	rac	
1859	+	
1860	-	
1861	rac	
1862	+	
1863	-	
1864	rac	
1865	+	
1866	-	
1867	rac	
1868	+	
1869	-	
1870	rac	
1871	+	

1872	-	
1873	rac	
1874	+	
1875	-	

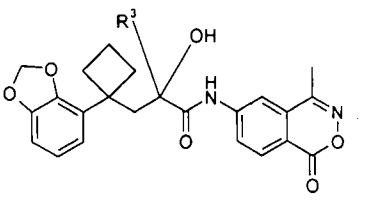


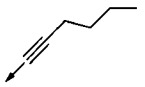
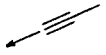
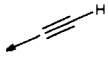
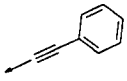
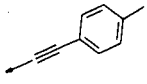
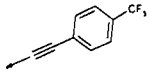
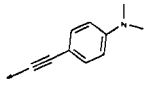
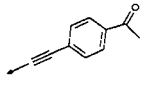
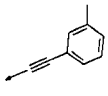
N°	Racémico o enantiómero	R3
1876	rac	
1877	-	
1878	+	
1879	rac	
1880	+	
1881	-	
1882	rac	
1883	+	
1884	-	
1885	rac	
1886	+	
1887	-	
1888	rac	
1889	+	
1890	-	
1891	rac	
1892	+	
1893	-	

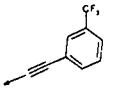
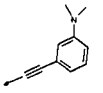
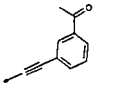
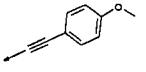
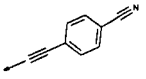
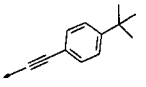
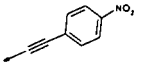
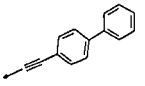
1894	rac	
1895	+	
1896	-	
1897	rac	
1898	+	
1899	-	
1900	rac	
1901	+	
1902	-	
1903	rac	
1904	+	
1905	-	
1906	rac	
1907	+	
1908	-	
1909	rac	
1910	+	
1911	-	
1912	rac	
1913	+	
1914	-	
1915	rac	
1916	+	
1917	-	

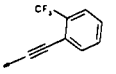
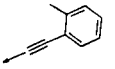
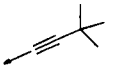
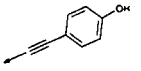
1918	rac	
1919	+	
1920	-	
1921	rac	
1922	+	
1923	-	
1924	rac	
1925	+	
1926	-	
1927	rac	
1928	+	
1929	-	
1930	rac	
1931	+	
1932	-	
1933	rac	
1934	+	
1935	-	
1936	rac	
1937	+	
1938	-	

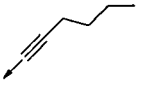
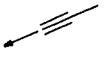
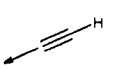
N°	Racémico o enantiómero	R3

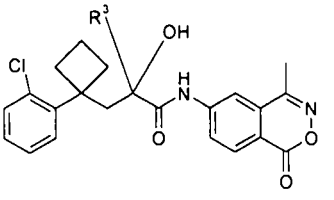


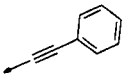
1939	rac	
1940	-	
1941	+	
1942	rac	
1943	+	
1944	-	
1945	rac	
1946	+	
1947	-	
1948	rac	
1949	+	
1950	-	
1951	rac	
1952	+	
1953	-	
1954	rac	
1955	+	
1956	-	
1957	rac	
1958	+	
1959	-	
1960	rac	
1961	+	
1962	-	
1963	rac	

1964	+	
1965	-	
1966	rac	
1967	+	
1968	-	
1969	rac	
1970	+	
1971	-	
1972	rac	
1973	+	
1974	-	
1975	rac	
1976	+	
1977	-	
1978	rac	
1979	+	
1980	-	
1981	rac	
1982	+	
1983	-	
1984	rac	
1985	+	
1986	-	
1987	rac	
1988	+	

1989	-	
1990	rac	
1991	+	
1992	-	
1993	rac	
1994	+	
1995	-	
1996	rac	
1997	+	
1998	-	
1999	rac	
2000	+	
2001	-	

N°	Racémico o enantiómero	R3
2002	rac	
2003	-	
2004	+	
2005	rac	
2006	+	
2007	-	
2008	rac	
2009	+	



2010	-	
2011	rac	
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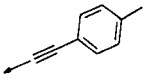
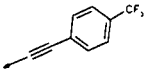
2013	-	
2014	rac	
2015	+	
2016	-	
2017	rac	
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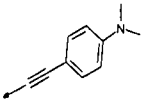
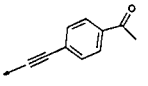
2019	-	
2020	rac	
2021	+	
2022	-	
2023	rac	
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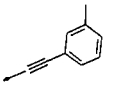
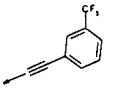
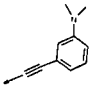
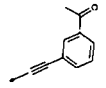
2025	-	
2026	rac	
2027	+	
2028	-	
2029	rac	
2030	+	
2031	-	
2032	rac	
2033	+	
2034	-	

2035	rac	
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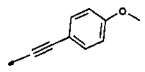
2037	-	
2038	rac	
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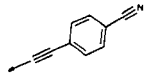
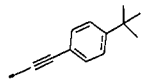
2040	-	
2041	rac	
2042	+	
2043	-	
2044	rac	
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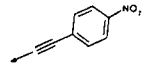
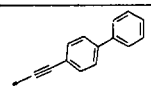
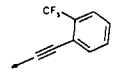
2046	-	
2047	rac	
2048	+	
2049	-	
2050	rac	
2051	+	
2052	-	
2053	rac	
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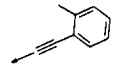
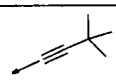
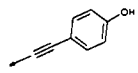
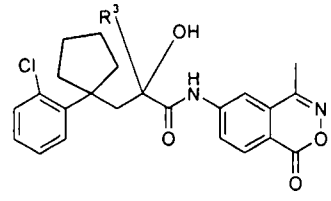
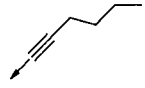
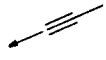
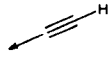
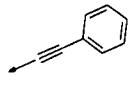
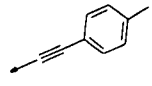
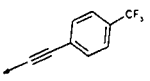
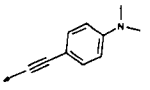
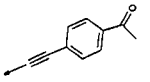
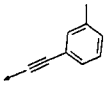
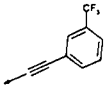
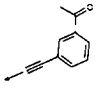
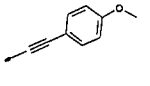
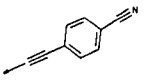
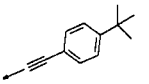
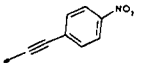
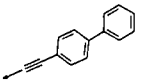
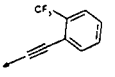
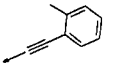
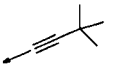
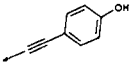
2055	-	
2056	rac	
2057	+	
2058	-	

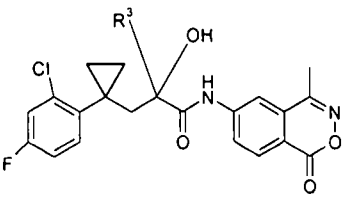
2059	rac	
2060	+	
2061	-	
2062	rac	
2063	+	
2064	-	

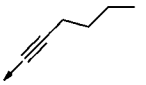
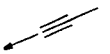
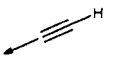
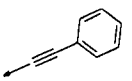


N°	Racémico o enantiómero	R3
2065	rac	
2066	-	
2067	+	
2068	rac	
2069	+	
2070	-	
2071	rac	
2072	+	
2073	-	
2074	rac	
2075	+	
2076	-	
2077	rac	
2078	+	

2079	-	
2080	rac	
2081	+	
2082	-	
2083	rac	
2084	+	
2085	-	
2086	rac	
2087	+	
2088	-	
2089	rac	
2090	+	
2091	-	
2092	rac	
2093	+	
2094	-	
2095	rac	
2096	+	
2097	-	
2098	rac	
2099	+	
2100	-	
2101	rac	
2102	+	
2103	-	

2104	rac	
2105	+	
2106	-	
2107	rac	
2108	+	
2109	-	
2110	rac	
2111	+	
2112	-	
2113	rac	
2114	+	
2115	-	
2116	rac	
2117	+	
2118	-	
2119	rac	
2120	+	
2121	-	
2122	rac	
2123	+	
2124	-	
2125	rac	
2126	+	
2127	-	



N°	Racémico o enantiómero	R3
2128	rac	
2129	-	
2130	+	
2131	rac	
2132	+	
2133	-	
2134	rac	
2135	+	
2136	-	
2137	rac	
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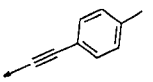
2139	-	
2140	rac	
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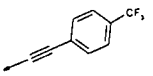
2142	-	
2143	rac	
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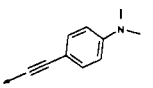
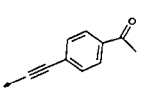
2145	-	
2146	rac	
2147	+	
2148	-	
2149	rac	

2150	+	
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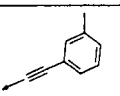
2152	rac	
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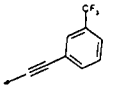
2155	rac	
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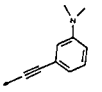
2158	rac	
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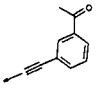
2161	rac	
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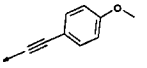
2163	-	
2164	rac	
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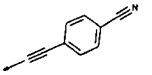
2167	rac	
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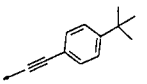
2170	rac	
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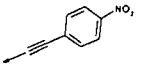
2172	-	
2173	rac	
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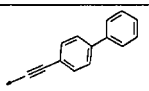
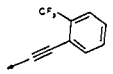
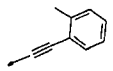
2175	-	
2176	rac	
2177	+	
2178	-	
2179	rac	
2180	+	
2181	-	
2182	rac	
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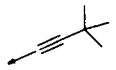
2184	-	
2185	rac	
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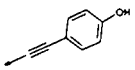
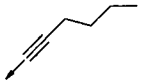
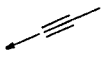
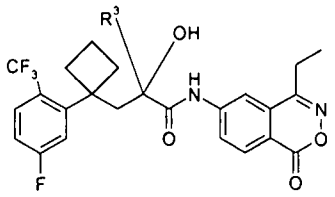
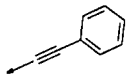
2188	rac	
2189	+	
2190	-	

N°	Racémico o enantiómero	R3
2191	rac	
2192	-	
2193	+	
2194	rac	
2195	+	



2196	-	
2197	rac	
2198	+	
2199	-	
2200	rac	
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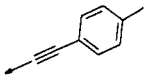
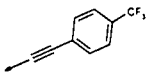
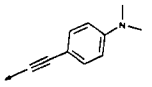
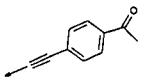
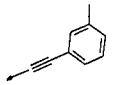
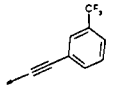
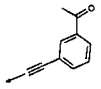
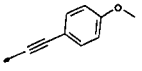
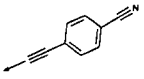
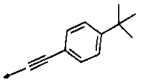
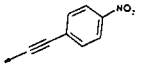
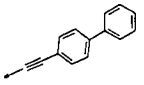
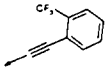
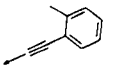
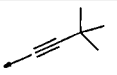
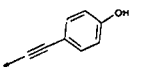
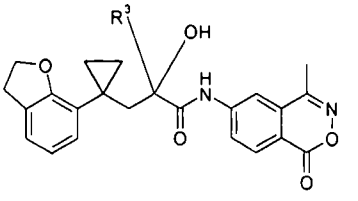
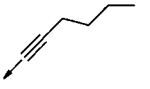
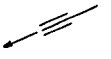
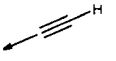
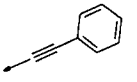
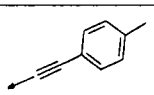
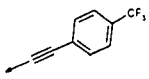
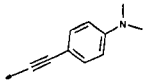
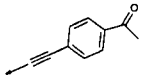
2202	-	
2203	rac	
2204	+	
2205	-	
2206	rac	
2207	+	
2208	-	
2209	rac	
2210	+	
2211	-	
2212	rac	
2213	+	
2214	-	
2215	rac	
2216	+	
2217	-	
2218	rac	
2219	+	
2220	-	

2221	rac	
2222	+	
2223	-	
2224	rac	
2225	+	
2226	-	
2227	rac	
2228	+	
2229	-	
2230	rac	
2231	+	
2232	-	
2233	rac	
2234	+	
2235	-	
2236	rac	
2237	+	
2238	-	
2239	rac	
2240	+	
2241	-	
2242	rac	
2243	+	
2244	-	

2245	rac	
2246	+	
2247	-	
2248	rac	
2249	+	
2250	-	
2251	rac	
2252	+	
2253	-	



N°	Racémico o enantiómero	R3
2254	rac	
2255	-	
2256	+	
2257	rac	
2258	+	
2259	-	
2260	rac	
2261	+	
2262	-	
2263	rac	
2264	+	
2265	-	

2266	rac	
2267	+	
2268	-	
2269	rac	
2270	+	
2271	-	
2272	rac	
2273	+	
2274	-	
2273	rac	
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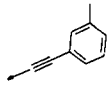
2277	-	
2278	rac	
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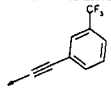
2280	-	
2281	rac	
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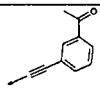
2283	-	
2284	rac	
2285	+	
2286	-	
2287	rac	
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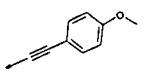
2289	-	
2290	rac	

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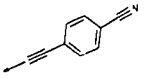
2292	-	
2293	rac	
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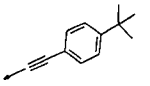
2296	rac	
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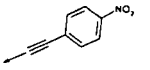
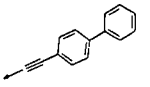
2298	-	
2299	rac	
2300	+	
2301	-	
2302	rac	
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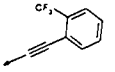
2304	-	
2305	rac	
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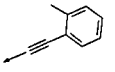
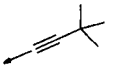
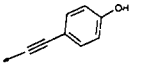
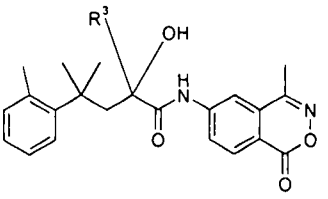
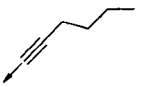
2307	-	
2308	rac	
2309	+	
2310	-	
2311	rac	
2312	+	
2313	-	
2314	rac	

200

2315	+	
2316	-	



N°	Racémico o enantiómero	R3
2317	rac	
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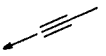
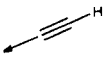
2319	+	
2320	rac	
2321	+	
2322	-	
2323	rac	
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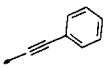
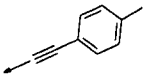
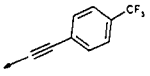
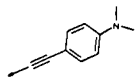
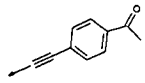
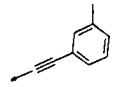
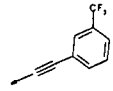
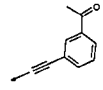
2325	-	
2326	rac	
2327	+	
2328	-	
2329	rac	
2330	+	
2331	-	
2332	rac	
2333	+	
2334	-	

2335	rac	
2336	+	
2337	-	
2338	rac	
2339	+	
2340	-	
2341	rac	
2342	+	
2343	-	
2344	rac	
2345	+	
2346	-	
2347	rac	
2348	+	
2349	-	
2350	rac	
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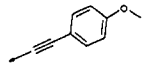
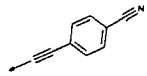
2652	-	
2353	rac	
2354	+	
2355	-	
2356	rac	
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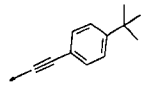
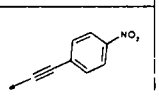
2358	-	
2359	rac	

2360	+	
2361	-	
2362	rac	
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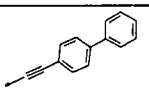
2364	-	
2365	rac	
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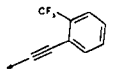
2367	-	
2368	rac	
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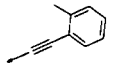
2371	rac	
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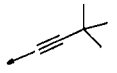
2373	-	
2374	rac	
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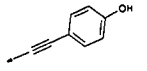
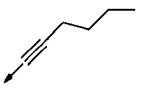
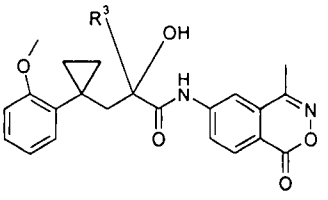
2376	-	
2377	rac	
2378	+	
2379	-	

N°	Racémico o enantiómero	R3
2380	rac	



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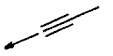
2382	+	
2383	rac	
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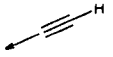
2386	rac	
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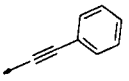
2389	rac	
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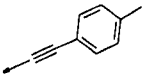
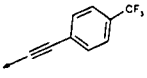
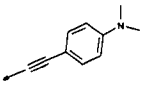
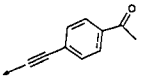
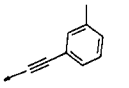
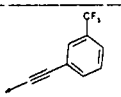
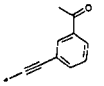
2391	-	
2392	rac	
2393	+	
2394	-	
2395	rac	
2396	+	
2397	-	
2398	rac	
2399	+	
2400	-	
2401	rac	
2402	+	
2403	-	
2404	rac	
2405	+	

2406	-	
2407	rac	
2408	+	
2409	-	
2410	rac	
2411	+	
2412	-	
2413	rac	
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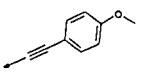
2416	rac	
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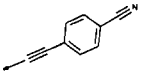
2419	rac	
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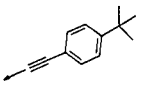
2422	rac	
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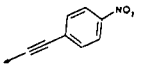
2425	rac	
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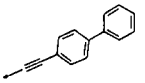
2428	rac	
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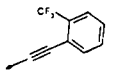
2431	rac	
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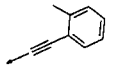
2434	rac	
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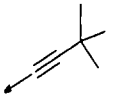
2437	rac	
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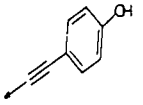
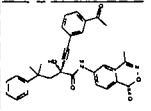
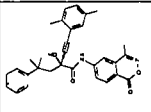
2440	rac	
2441	+	
2442	-	

N°	Racémico o enantiómero	Estructura
2443	rac	
244	-	
2445	+	
2446	rac	
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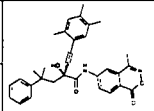
2448	-	
2449	rac	
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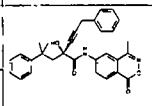
2451	-	
2452	rac	
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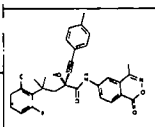
2455	rac	
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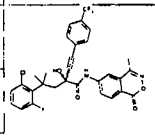
2458	rac	
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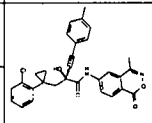
2461	rac	
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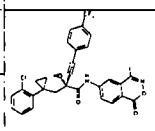
2464	rac	
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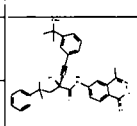
2467	rac	
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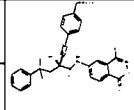
2470	rac	
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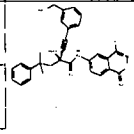
2473	rac	
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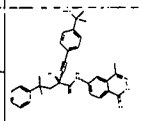
2475	-	
2476	rac	
2477	+	
2478	-	

Caracterización biológica de los compuestos de acuerdo con la invención

La identificación de los moduladores de receptor de progesterona se puede llevar a cabo con ayuda de métodos sencillos y programas de ensayo conocidos para el técnico. Para ello se puede, por ejemplo, incubar el compuesto que se desea ensayar junto con un gestágeno en un sistema de ensayo para receptores de progesterona y comprobar, si en este sistema de ensayo se modifica el efecto de la progesterona en presencia del modulador.

Las sustancias de la fórmula general I de la invención fueron ensayadas en los siguientes modelos:

Ensayo de fijación de receptor de progesterona

Medición de la afinidad de fijación del receptor:

La afinidad de fijación del receptor fue determinada por la fijación competitiva de una hormona de fijación específica marcada ^{3}H (tracer) y del compuesto a ensayar en receptores en el citosol de órganos-objetivo de animales. Se intentó lograr la saturación del receptor y el equilibrio de la reacción.

El tracer y concentraciones crecientes del compuesto a

ensayar (competitor) fueron co-inacubados a 0-4°C durante 18 h con la fracción de citosol que contenía el receptor. Después de separar el tracer no fijado con suspensión de carbón/dextrano se midió la proporción de tracer de cada concentración y se determinó el IC_{50} a partir de la serie de concentraciones. Como cociente de los valores IC_{50} de la sustancia de referencia y el compuesto a ensayar (x 100%) se calculó la afinidad de fijación molar relativa (RBA) (RBA de la sustancia de referencia = 100%).

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

Receptor de progesterona:

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

Receptor de glucocorticoide:

Citosol de timo de rata adrenalectomada, timos conservados a -30°C; buffer: TED. Tracer: ^{3}H-dexametasona, 20 nM; Sustancia de referencia: dexametasona.

Las afinidades de fijación de receptor relativas (valores RBA) de los compuestos de la fórmula general (I) de la invención en el receptor de progesterona son de entre 3 y 100 %, referido a la progesterona. En el receptor de

glucocorticoide, los valores RBA son del rango de 3 a 30 %, referido a dexametasona.

Los compuestos de acuerdo con la invención tienen, por lo tanto, una elevada afinidad con el receptor de progesterona, pero escasa afinidad con el receptor de glucocorticoide.

Antagonismo con el receptor de progesterona PR-B

El ensayo de transactivación se lleva a cabo de la manera que se describe en el documento WO 02/054064.

Agonismo con el receptor de progesterona PR-B

El ensayo de transactivación se lleva a cabo como se describe 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	**Efecto antagónista**		**Efecto agonista**	
	IC_{50} [nM]	Eficacia [%]	EC_{50} [nM]	Eficacia [%]
5	0,2	86	0,2	10
14	6	53	7	35
16	0,7	82	0,5	13
17b	0,03	88	no determinado.	7
18	0,2	89	No det.	8
24	2	100		0
35	2	100		0

Dosificación

Para el uso de acuerdo con la invención, los moduladores de receptor de progesterona pueden ser administrados por vía oral, enteral, parenteral o transdérmica.

En general, se pueden esperar resultados satisfactorios en el tratamiento de las indicaciones mencionadas más arriba cuando se administran dosis diarias de 1 µg a 500 mg del compuesto de acuerdo con la invención.

Las dosificaciones apropiadas de los compuestos de la invención para el tratamiento de la endometriosis, de leiomiomas del útero y sangrados disfuncionales en humanos así como para el control de la fertilidad y la terapia de sustitución hormonal son de 50 µg a 500 mg por día, según la edad y constitución física del paciente, pudiendo aplicarse la dosis diaria necesaria en una o varias tomas.

Para el tratamiento de carcinomas de mama, la dosis diaria de los compuestos de la invención es de 10 mg a 1000 mg.

Los productos farmacéuticos basados en de los nuevos compuestos se formulan de manera conocida *per se:* procesando el ingrediente activo con los vehículos, cargas, agentes de desintegración, aglutinantes, humectantes, lubricantes, absorbentes, diluyentes, correctores del sabor, colorantes etc, usuales en la galénica y se lleva a la forma de

aplicación deseada. Nos remitimos para esto, a Remington's Pharmaceutical Science, 15th ed. Mack Publishing Company, East Pennsylvania (1980).

Para la aplicación oral se pueden usar especialmente tabletas, tabletas recubiertas, grageas, cápsulas, píldoras, polvos, granulados, pastillas, suspensiones, emulsiones o soluciones.

Para la aplicación parenteral se pueden usar preparaciones inyectables o para infusión.

Para inyección intraarticular se pueden usar suspensiones de cristales preparadas debidamente.

Para inyección intramuscular se pueden usar soluciones o suspensiones inyectables acuosas u oleosas y preparaciones de depósito apropiadas.

Para la aplicación rectal, los nuevos compuestos se pueden usar en forma de supositorios, cápsulas, soluciones (p. ej. en forma de enema) y ungüentos, tanto para terapias locales como sistémicas.

Además, también mencionaremos preparaciones para aplicación vaginal.

Para la aplicación pulmonar de los nuevos compuestos, se los puede usar en forma de aerosoles o inhalantes.

Para la aplicación transdérmica son posibles los parches o para la aplicación tópica, formulaciones en geles, ungüentos, ungüentos grasos, cremas, pastas, polvos, leches

y tinturas. En estas preparaciones, la dosificación de los compuestos de la fórmula general I deberá ser de 0,01% - 20%, para lograr un efecto farmacológico suficiente.

Las respectivas tabletas se pueden obtener, por ejemplo, mezclando la sustancia activa con coadyuvantes conocidos tales como diluyentes inertes como dextrose, azúcar, sorbita, manita, polivinilpirrolidona, agentes de disgregación como almidón de maíz o ácido algínico, aglutinantes como almidón o gelatina, agentes deslizantes como estearato de magnesio o talco y/o sustancias para obtener un efecto de depósito, como carboxilpolimetileno, carboxilmetilcelulosa, ftalato de acetato de celulosa o acetato de polivinilo. Las tabletas también pueden comprender varias capas.

De la misma manera, las tabletas recubiertas se pueden preparar recubriendo núcleos preparados en forma análoga a las tableas con productos de recubrimientos para tabletas habituales, por ejemplo polivinilpirrolidona o goma-laca, goma arábiga, talco, óxido de titanio o azúcar. En estos casos, la envoltura de la tableta recubierta también puede comprender varias capas, para lo cual se usan los coadyuvantes mencionados más arriba para las tabletas.

Las soluciones o suspensiones de los compuestos de la fórmula general I de la invención pueden contener además, sustancias correctoras del sabor como sacarina, ciclamato o

azúcar, así como sustancias aromáticas como vainillina o extracto de naranja. También pueden contener mejoradores de la suspensión como carboximetilcelulose sódica o agentes conservantes como p-hidroxibenzoato.

Las cápsulas que contienen compuestos de la fórmula general I pueden prepararse p.ej., mezclando el/los compuestos de la fórmula general I con un vehículo inerte como azúcar de leche o sorbita y envasando en cápsulas de gelatina.

Se pueden preparar supositorios apropiados, por ejemplo, mezclando con vehículos destinados al efecto como grasas neutras o polietilenglicol o sus derivados.

Debido a su efecto antagonista o parcialmente agonista, los compuestos de la fórmula general (I) de la invención o sus sales aceptables para uso farmacéutico se pueden usar para la preparación de un medicamento, especialmente para el tratamiento y la prevención de enfermedades ginecológicas como endometriosis, leiomiomas del útero, sangrados disfuncionales y de la dismenorrea. También pueden ser usados en casos de irregularidades hormonales, para desencadenar la menstruación y solos o en combinación con prostaglandinas y/o oxitocina, para inducir el parto.

Los compuestos de la fórmula general (I) de la invención o sus sales aceptables para uso farmacéutico también son apropiados para obtener preparaciones

contraceptivas para la mujer (véase también WO 93/23020, WO 93/21927).

Los compuestos de la invención o sus sales aceptables para uso farmacéutico también se pueden usar solos o en combinación con moduladores selectivos de receptor de estrógeno (SERM) para la terapia de sustitución hormonal femenina.

Además, los mencionados compuestos ejercen un efecto antiproliferativo en tumores hormona-dependientes. Por lo tanto son apropiados para la terapia de carcinomas hormona-dependientes tales como por ejemplo, carcinomas de mama, de próstata y del endometrio.

Los compuestos de la invención o sus sales aceptables para uso farmacéutico pueden usarse para el tratamiento de carcinomas hormona-dependientes. Tanto en la terapia *first-line*, como en la terapia *second-line*, particularmente después que falla el tamoxifen.

Los compuestos que tienen efecto antagonista o parcialmente agonista de la fórmula general (I) de la invención o sus sales aceptables para uso farmacéutico también pueden usarse en combinación con compuestos de efecto antiestrógeno (antagonista de receptor de estrógeno o inhibidor de la aromatasa) o con moduladores selectivos del receptor de estrógeno (SERM) para obtener preparados farmacéuticos para el tratamiento de tumores hormona-

dependientes. Para el tratamiento de la endometriosis o de leiomiomas del útero, los compuestos de la invención también se pueden usar con SERM's o un antiestrógeno antagonista de receptor de estrógeno o inhibidores de la aromatasa. En el tratamiento de tumores hormona-dependientes, el modulador de receptor de progesterona y el antiestrógeno (antagonista de receptor de estrógeno o inhibidor de la aromatasa) o el SERM también pueden preverse para administración simultánea o sequencial. En la administración secuencial se prefiere administrar primeramente el antiestrógeno (antagonista de receptor de estrógeno o inhibidor de la aromatasa) o el SERM y a continuación, el modulador del receptor de progesterona.

Para combinar con los moduladores de receptor de progesterona no esteroides de la invención se pueden usar, por ejemplo, los siguientes antiestrógenos (antagonista de receptor de estrógeno o inhibidor de la aromatasa) o SERMs: Tamoxifeno, 5-(4-{5-[(RS)-(4,4,5,5,5-pentafluoropentil sulfinil]pentiloxi}fenil)-6-fenil-8,9-dihidro-7H-benzociclohepten-2-ol (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-pentafluorpentil)sulfanil]propil}amino)pentil] estra-1,3,5(10)-trien-3,17beta-diol (WO98/07740), 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 (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 (WO 03/045972), clomifen, raloxifen, así como otros compuestos con efecto antiestrógeno e inhibidores de la aromatasa tales como por ejemplo, fadrozol, formestano, letrozol, anastrozol o atamestano.

Finalmente, la presente invención también se refiere al uso de los compuestos de la fórmula general I, opcionalmente junto con in antiestrógeno o SERM, para preparar un medicamento.

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

Estas composiciones farmacéuticas y medicamentos pueden destinarse a la aplicación oral, rectal, vaginal, subcutánea, percutánea, intravenosa o intramuscular. Además de vehículos y/o diluyentes, contienen al menos un compuesto de la invención.

Los medicamentos de la invención se preparan de manera conocida, en dosificaciones apropiadas, con los vehículos o diluyentes sólidos o líquidos habituales y los coadyuvantes

de uso técnico-farmacéutico corriente, según la forma de aplicación deseada. Las composiciones preferidas comprenden una forma de administración apropiada para la aplicación oral. Tales formas de administración son, p.ej., tabletas, tabletas recubiertas, grageas, cápsulas, píldoras, polvos, soluciones o suspensiones o también formas de depósito.

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

También se pueden usar composiciones de administración parenteral como soluciones inyectables. También mencionaremos preparaciones en forma de supositorios o de óvulos para uso vaginal.

Los siguientes ejemplos sirven de explicación más detallada del objeto de la invención, sin limitar el alcance de la invención a los mismos.

La preparación de los compuestos de partida: 6-[4-(2-cloro-5-fluorofenil)-4-metil-2-oxovaleroilamino]-4-metil-2,3-benzoxazin-1-ona, 6-[4-(2-cloro-4-fluorofenil)-4-metil-2-oxovaleroilamino]-4-metil-2,3-benzoxazin-1-ona y 6-{3-[1-(2-clorofenil)-ciclopentil]-2-oxopropionilamino}-4-metil-2,3-benzoxazin-1-ona han sido descritos en la patente US2002/0077356; el compuesto 6-[4-(2,3-dihidro-7-benzofuranil)-4-metil-2-oxo-pentanoil-amino]-4-metil-2,3-benzoxazinona, en la patente US 6,323,199B1 (en el ejemplo

87), el compuesto 6-(4-metil-4-fenil-2-oxovaleroilamino)-4-metil-2,3-benzoxazin-1-ona in la patente WO 199854159 y el compuesto 6-[3-[1-(2-fluoro-5-trifluorometilfenil) ciclopropil]-2-oxopropionilamino]-4-metil-2,3-benzoxazin-1-ona en la patente WO 200375915.

Métodos generales

1-(benzo[1,3]dioxol-4-il)-1-metiletanol

Se mezclaron 25,5 g 4-acetilbenzo[1,3]dioxol con 57,2 ml solución de cloruro de metilmagnesio (3M en THF) en 375 ml THF a temperatura ambiente bajo argón. Se agitó 16 h a temperatura ambiente y se vertió sobre a hielo / ácido clorhídrico 2N. Luego se extrajo con acetato de etilo y la fase orgánica se lavó con agua y salmuera y se secó (Na_2SO_4). Se obtuvieron 27,89 g 1-[benzo(1,3)dioxol-4-il]-1-metiletanol en forma de aceite castaño.

^{1H}-NMR ($CDCl_3$, ppm) = 1,6 (s, 6H), 5,95 (s, 2H), 6,76 (dd, 1H), 6,82 (t, 1H), 6,91 (dd, 1H)

Ácido 4-(benzo[1,3]dioxol-4-il)-4-metil-2-oxo-pentanoico

Se mezclaron 9,5 g 1-(benzo[1,3]dioxol-4-il)-1-metiletanol y 14,2 g éster etílico del ácido 2-trimetilsililoxi-acrílico en 200 ml diclorometano a -70 °C con 47 ml cloruro de estaño(IV). Después de 15 minutos se vertió la solución sobre solución de carbonato de potasio. Después de extraer con dietiléter se lavó la fase orgánica con agua, se secó y se concentró.

14,4 g del éster etílico del ácido 4-(benzo[1,3]dioxol-4-il)-4-metil-2-oxo-pentanoico así obtenido se agitaron con 150 ml hidróxido de sodio 1M y 300 ml metanol durante 10 horas a temperatura ambiente. El metanol se retiró luego al vacío y la solución restante se extrajo con dietiléter. La fase acuosa se acidificó con ácido clorhídrico 1M y se extrajo con dietiléter. Después de secar y concentrar se obtuvieron 11,1 g ácido 4-(benzo[1,3]dioxol-4-il)-4-metil-2-oxo-pentanoico en forma de aceite amarillento.

MS (ei) m/e: M^+ = 251

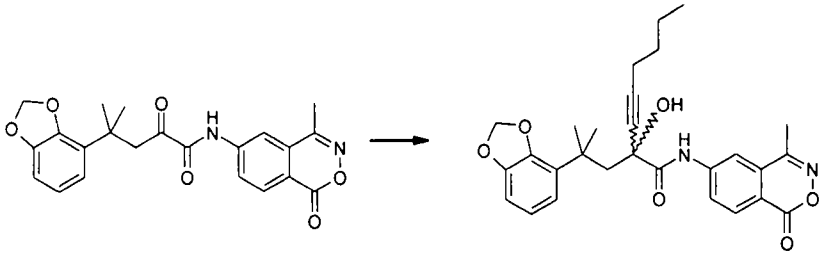
6-[4-(benzo[1,3]dioxol-4-il)-4-metil-2-oxo-valeroil-amino]-4-metil-2,3-benzoxazin-1-ona

10 g ácido 4-(benzo[1,3]dioxol-4-il)-4-metil-2-oxo-pentanoico se disolvieron en 125 ml dimetilacetamida y se mezclaron bajo argón a -0°C con 3,5 ml cloruro de tionilo. Después de agitar 20 minutos a -3 a +3°C se agregaron 7,6 g 6-amino-4-metil-2,3-benzoxazin-1-ona (WO00/32584). Se agitó 96 horas a temperatura ambiente, luego se mezcló con agua, se extrajo con acetato de etilo, se lavó la fase orgánica con agua, se secó (Na_2SO_4) y después de concentrar el solvente y cromatografía del producto bruto con gel de sílice y hexano / etilacetato (100:0 -> 60:40) se obtuvieron 6,56 g 6-[4-(benzo[1,3]dioxol-4-il)-4-metil-2-oxo-valeroil-amino]-4-metil-2,3-benzoxazin-1-ona en forma de sólido beige.

Punto de fusión = 165-166°C, MS (ei) m/e: M^+ = 409

Ejemplos de síntesis

(-)-6-{2-[2-(2,3-(metilendioxi)fenil)-2-metilpropil]-2-hidroxi-oct-3-inaoil}-4-metil-2,3-benzoxazin-1-ona 1 y (+)-6-{2-[2-(2,3-(metilendioxi)fenil)-2-metilpropil]-2-hidroxi-oct-3-inaoil}-4-metil-2,3-benzoxazin-1-ona 2

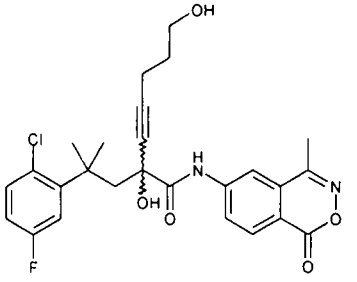


Se mezcló una solución de 1-hexina (0,5 ml) en THF (4 ml) a -78°C con nBuLi (0,7 ml, 1,6M en hexano). Se agitó 20 min a -78°C, se agregó 1-(benzo[1,3]dioxol-4-il)-4-metil-2-oxo-valeroil-amino]-4-metil-2,3-benzoxazin-1-ona (192 mg) y se agitó 4 h a -78°C. Luego se adicionó agua y se dejó calentar a temperatura ambiente. Después de extracción con acetato de etilo, se lavó con solución saturada de cloruro de sodio, se secó sobre sulfato de sodio y se purificó por cromatografía de columna con gel de sílice. Se obtuvieron 82 mg de una espuma blanca, que luego se convirtió por HPLC quiral preparativa(Columna Chiralpak AD 250x10mm, eluyente: acetonitrilo/ agua 55/45 v/v, fluencia 4,7 mL/min, temperatura 40 °C, tiempo de retención: 12,2 min (+)-enantiómero, 15,7 min (-)-enantiómero) en los compuestos (-)-6-{2-[2-(2,3-(metilendioxi)fenil)-2-metilpropil]-2-

hidroxi-oct-3-inaoil}-4-metil-2,3-benzoxazin-1-ona (ejemplo 1) y (+)-6-{2-[2-(2,3-(metilendioxi)fenil)-2-metilpropil]-2-hidroxi-oct-3-inaoil}-4-metil-2,3-benzoxazin-1-ona (ejemplo 2).

^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 0,91 (t, J = 7,2 Hz, 3H, CH3), 1,32 - 1,49 (m, 4H), 1,55 (s, 3H), 1,58 (s, 3H), 2,17 (t, J = 7,2 Hz, 2H), 2,56 (s, 3H, CH3), 2,59 (d, J = 14,4 Hz, 1H), 2,74 (d, J = 14,8 Hz, 1H), 2,80 (s, 1H, OH), 5,94 - 5,96 (m, 2H), 6,46 - 6,49 (m, 1H), 6,64 (t, J = 7,8 Hz, 1H), 7,47 - 7,49 (m, 1H), 8,25 - 8,28 (m, 1H), 8,76 (s, 1H, NH). $C_{28}H_{30}N_2O_6$ (490,6):

rac-6-{2-[2-(2-cloro-5-fluorofenil)-2-metilpropil]-2,7-dihidroxi-hept-3-inaoil}-4-metil-2,3-benzoxazin-1-ona 3



Etapa A: La conversión de 5-(*tert*-butildimetilsililoxo)pent-1-ina (531 mg), nBuLi (0,7 ml, 1,6 M en hexano) y 6-[4-(2-cloro-5-fluorofenil)-4-metil-2-oxovaleroilamino]-4-metil-2,3-benzoxazin-1-ona (207 mg) a -78°C como se describió en el ejemplo 1 dio, después de cromatografía de columna con gel de sílice, un aceite incoloro (86 mg).

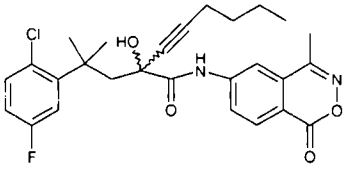
Etapa B: Se agita el aceite obtenido en THF (3 ml) bajo

argón a temperatura ambiente (3 h). Después de agregar agua, de extraer con acetato de etilo, lavar con solución saturada de sal común, se secó con sulfato de sodio. La purificación por cromatografía de columna con gel de sílice dio el compuesto del título en forma de espuma blanca (43 mg).

^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 1,58 (s, 3H, Me), 1,59 (s, 3H, Me), 1,71 - 1,74 (m, 2H, CH_2), 2,2 - 2,3 (m, 2H), 2,56 (s, 3H, CH_3), 2,75 (d, J = 15,2 Hz, 1H, CH), 2,92 (d, J = 14,8 Hz, 1H, CH), 3,26 (s, 1H, OH), 3,74 - 3,78 (m, 2H), 6,67 - 6,78 (m, 1H), 7,09 - 7,19 (m, 2H), 7,66 - 7,69 (m, 2H), 8,20 - 8,21 (m, 1H), 8,27 - 8,29 (m, 1H), 8,99 (s, 1H, NH).

$C_{26}H_{26}ClFN_2O_5$ (501,0): LC-MS: m/z = 501 [M + H^+].

rac-6-{2-[2-(2-cloro-5-fluorofenil)-2-metilpropil]-2-hidroxi-oct-3-inaoil}-4-metil-2,3-benzoxazin-1-ona 4

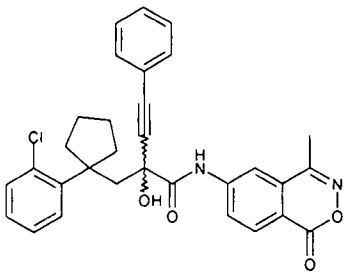


La conversión de 1-hexina (0,6 ml), nBuLi (0,7 ml, 1,6 M en hexano) y 6-[4-(2-cloro-5-fluorofenil)-4-metil-2-oxovaleroilamino]-4-metil-2,3-benzoxazin-1-ona (207 mg) a -78°C como se describió en el ejemplo 1 dio, después de cromatografía de columna con gel de sílice y cromatografía preparativa de capa delgada, un aceite denso (12 mg).

^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 0,90 (t, J = 7,2 Hz, 3H, Me), 1,32 - 1,47 (m, 4H), 1,57 (s, 3H, Me), 1,62 (s, 3H, Me),

2,13 (t, J = 7,2 Hz, $CH_2C{\equiv}C$), 2,56 (s, 3H, Me), 2,81 - 2,95 (m, 3H), 6,68 - 6,71 (m, 1H), 7,11 - 7,17 (m, 2H), 7,56 - 7,58 (m, 1H), 8,21 (d, J = 2,0 Hz, 1H), 8,29 (d, J = 12,6 Hz, 1H), 8,73 (br. s., 1H, NH). $C_{27}H_{28}ClFN_2O_4$ (499,0): LC-MS: m/z = 499 $[M + H^+]$.

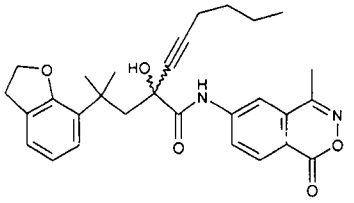
rac-6-{2-[(2-clorofenil)-ciclopentil]metil-2-hidroxi-4-fenil-but-3-inaoilamino}-4-metil-2,3-benzoxazin-1-ona 5



Se agregó fenilacetilida de litio (0,65 ml, 1M en THF) a 6-{3-[1-(2-clorofenil)-ciclopentil]-2-oxopropionilamino}-4-metil-2,3-benzoxazin-1-ona (110 mg) a -78°C y se dejó calentar durante la noche a temperatura ambiente. Después de preparar como se describió en el ejemplo 1 y cromatografía de columna con gel de sílice y después de secar en la bomba de aceite, se obtuvieron los compuestos del título en forma de espuma, (54 mg).

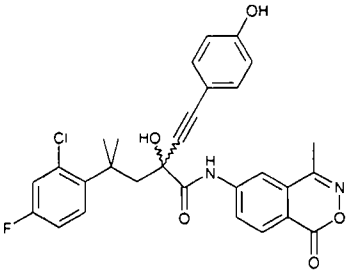
^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 1,59 - 1,85 (m, 5H), 2,18 - 2,35 (m, 3H), 2,54 (s, 3H, Me), 2,7 - 3,09 (3H), 6,94 - 7,58 (m, 10H), 8,18 (d, J = 1,1 Hz), 8,25 (d, J = 8,6 Hz, 1H), 8,81 (br. s., 1H, NH). $C_{31}H_{27}ClN_2O_4$ (526,0): HPLCMS: m/z = 526 [M], Pureza 97%.

6-{2-[2-(2,3-dihidro-7-benzofuranil)-2-metilpropil]-2-hidroxi-3-octinoilamino}-4-metil-2,3-benzoxazin-1-ona 6



La conversión de 1-hexina (0,4 ml), nBuLi (0,7 ml, 1,6 M en hexano) y 6-[4-(2,3-dihidro-7-benzofuranil)-4-metil-2-oxopentanoilamino]-4-metil-2,3-benzoxazin-1-ona (99,5 mg) a -78°C en THF (3 ml) como se describió en el ejemplo 1 dio, después de cromatografía de columna con gel de sílice y secar al vacío, un aceite incoloro cristalizado(42 mg). ^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 0,89 (t, J =7,2 Hz, 3H, Me), 1,35 - 1,56 (m, 10H), 2,14 - 2,18 (m, 2H), 2,56 (s, 3H, Me), 2,66 (d, J =14,8 Hz, 1H), 2,73 (d, J = 14,8 Hz, 1H), 3,0 - 3,2 (m, 2H), 3,27 (s, 1H), 4,57 (t, J = 9,3 Hz, 2H), 6,75 (t, J = 7,5 Hz, 1H), 6,95 (d, J = 6,3 Hz, 1H), 7,05 (d, J = 7,8 Hz, 1H), 7,50 - 7,52 (m, 1H), 8,23 - 8,29 (m, 2H), 8,78 (br. s., NH). $C_{29}H_{32}ClN_2O_5$ (488): LC-MS: m/z = 489 [M + H^+].

rac-6-{4-(2-cloro-4-fluorofenil)-2-hidroxi-2-[(4-hidroxifenil)etinil]-4-metil pentanoilamino}-4-metil-2,3-benzoxazin-1-ona 7



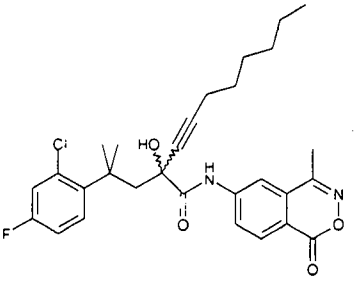
Etapa A: Se convirtió una suspensión del compuesto del ejemplo 10 (57,8 mg), trifenilfosfina (6,8 mg), yoduro de cobre (5 mg), acetato de 4-yodofenilo (51 mg), 5 mg acetato de paladio en THF (1 ml) y trietilamina (3 ml) durante 1 h en baño de ultrasonido bajo argón. Se agregó solución acuosa saturada de cloruro de amonio, se extrajo con acetato de etilo, se lavó con agua y con solución de sal común. Después de secar con sulfato de sodio se concentró y se purificó por cromatografía de columna con gel de sílice. Se obtuvo un sólido blanco (46,7 mg).

Etapa B: Se agitó una suspensión del compuesto de la etapa A (46,7 mg) y bicarbonato de sodio (128 mg) en metanol a temperatura ambiente durante 6 h bajo argón. Luego se agregó una punta de espátula de bicarbonato de sodio y se agitó durante la noche. Se diluyó con acetato de etilo, se agregó agua y se extrajo después de separar las fases con acetato de etilo. Después de lavar las fases orgánicas reunidas con solución de sal común, de secar sobre sulfato de sodio, de concentrar y de purificar por cromatografía de columna con

gel de sílice, se obtuvieron los compuestos del título en forma de aceite denso (29 mg).

^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 1,63 (s, 3H, Me), 1,69 (s, 3H, Me), 2,56 (s, 3H, Me), 2,94 - 3,01 (m, 3H), 5,48 (br. s, 1H, OH), 6,74 - 6,77 (m, 2H), 6,84 - 6,93 (m, 2H), 7,21 - 7,25 (m, 2H), 7,43 (dd, J = 9,0, 6,1 Hz, 1H), 7,57 - 7,59 (dd, J = 8,6, 2,3 Hz, 1H), 8,22 - 8,23 (m, 1H), 8,31 (d, J = 8,6 Hz, 1H), 8,80 (br. s, 1H, NH). $C_{29}H_{24}ClFN_2O_5$ (534,98): LC-MS: m/z = 535 [M + H^+].

rac-6-{2-[2-(2-cloro-4-fluorofenil)-2-metilpropil]-2-hidroxi-dec-3-inaoilamino}-4-metil-2,3-benzoxazin-1-ona 8

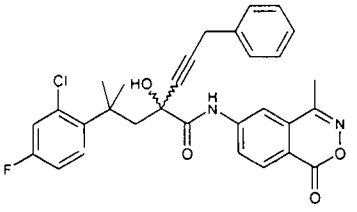


La conversión de 1-octina (0,4 ml), nBuLi (0,6 ml, 1,6 M en hexano) y 6-[4-(2-cloro-4-fluorofenil)-4-metil-2-oxo-valeroilamino]-4-metil-2,3-benzoxazin-1-ona (110 mg) en THF (3 ml) a -78°C como se describió en el ejemplo 1 dio, después de cromatografía de columna con gel de sílice, un sólido blanco (25 mg).

^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 0,87 (t, J = 7,0 Hz, 3H), 1,26 - 1,46 (m, 8H), 1,58 (s, 3H, Me), 1,63 (s, 3H, Me), 2,12 (t, J = 7,0 Hz, $CH_2C{\equiv}C$), 2,56 (s, 3H, Me)2,79 - 2,91 (m, 3H),

6,92 - 6,95 (m, 2H), 7,40 (dd, J = 8,9, 6,3 Hz, 1H), 7,53 (dd, J = 8,6, 1,9 Hz, 1H), 8,21 (d, J = 1,9 Hz, 1H), 8,30 (d, J = 8,6 Hz, 1H), 8,71 (br. s., 1H, NH); $C_{29}H_{32}ClFN_2O_4$ (527,0): LC-MS: m/z = 527 [M + H^+].

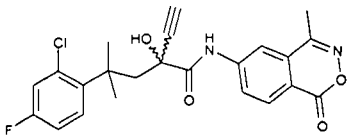
rac-6-{2-[2-(2-cloro-4-fluorofenil)-2-metilpropil]-2-hidroxi-5-fenilpent-3-inaoilamino}-4-metil-2,3-benzoxazin-1-ona 9



La conversión de 3-fenilo-1-propina (0,17 ml), nBuLi (0,51 ml, 1,6 M en hexano) y 6-[4-(2-cloro-4-fluorofenil)-4-metil-2-oxovaleroilamino]-4-metil-2,3-benzoxazin-1-ona (140 mg) en THF (3 ml) a -78°C como se describió en el ejemplo 1 dio, después de cromatografía de columna con gel de sílice y secar al vacío, una espuma blanca (116 mg).

^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 1,59 (s, 3H, Me), 1,61 (s, 3H, Me), 2,55 (s, 3H, Me), 2,79 - 2,95 (m, 3H), 3,4 - 3,6 (m, 2H, $CH_2C{\equiv}C$), 6,8 - 6,93 (m, 2H), 7,23 - 7,42 (m, 7H), 8,15 (d, J = 2,3 Hz, 1H), 8,27 (d, J = 8,6 Hz, 1H), 8,64 (br. s., 1H, NH). $C_{30}H_{26}ClFN_2O_4$ (533,0): LC-MS: m/z = 533 [M + H^+].

rac-6-{4-(2-cloro-4-fluorofenil)-2-etinil-2-hidroxi-4-metil-pentanoilamino}-4-metil-2,3-benzoxazin-1-ona 10

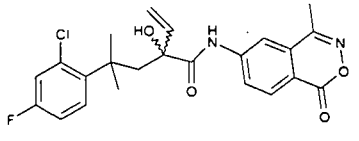


Se adicionó bromuro de etinilmagnesio (2,2 ml, 0,5 M en THF) a una solución helada de 6-[4-(2-cloro-4-fluorofenil)-4-metil-2-oxovaleroilamino]-4-metil-2,3-benzoxazin-1-ona (208 mg) en THF (4 ml). Se dejó calentar la solución de reacción bajo argón durante 3 h a temperatura ambiente. Después de preparar como se describió en el ejemplo 1 y cromatografía de columna con gel de sílice y después de secar en la bomba de aceite, se obtuvieron los compuestos del título en forma de espuma, (84 mg).

^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 0,8 - 0,9 (m, 1H), 1-58 (s, 3H, Me), 1,65 (s, 3H, Me), 2,56 - 2,96 (6H), 6,86 - 6,94 (m, 2H), 7,41 (dd, J = 9,0, 6,2 Hz, 1H), 7,56 (dd, J = 8,6, 1,9 Hz, 1H), 8,19 (d, J = 1,9 Hz, 1H), 8,31 (d, J = 8,6 Hz, 1H), 8,63 (br. s., 1H, NH).

$C_{23}H_{20}ClFN_2O_4$ (542,9): LC-MS: m/z = 543 [M + H^+].

rac-6-{4-(2-cloro-4-fluorofenil)-2-hidroxi-4-metil-2-vinil-pentanoilamino}-4-metil-2,3-benzoxazin-1-ona 11

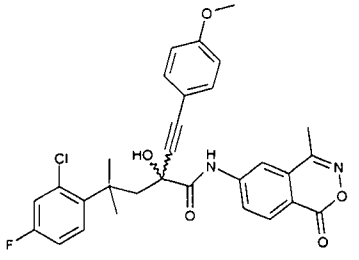


Se roció una solución de bromuro de vinilmagnesio (0,5 ml, 1M en THF) a -78°C sobre 6-[4-(2-cloro-4-fluorofenil)-4-metil-2-oxovaleroilamino]-4-metil-2,3-benzoxazin-1-ona (103

mg) en THF (3 ml) y se dejó calentar a temperatura ambiente durante la noche bajo argón. Se adicionó solución de cloruro de amonio acuosa, se extrajo con acetato de etilo y se lavó con solución saturada de cloruro de sodio. Después de secar con sulfato de sodio se concentró en el evaporador rotativo, se purificó por cromatografía de columna con gel de sílice y se obtuvo los compuestos del título en forma de aceite cristalizado (18 mg).

^{1}H-NMR (ppm, $CDCl_3$, 400 MHz, señales seleccionadas): 1,53 (s, 3H, Me), 1,57 (s, 3H, Me), 2,35 (s, 1H), 2,56 (s, 3H, Me), 2,74 (d, J = 15,3 Hz, 1H), 2,89 (d, J = 15,3 Hz, 1H), 5,15 (d, J = 10,5 Hz, 1H), 5,27 (d, J = 17,6 Hz, 1H), 6,10 (dd, J = 17,2, 10,6 Hz, 1H), 6,81 - 6,86 (m, 1H),

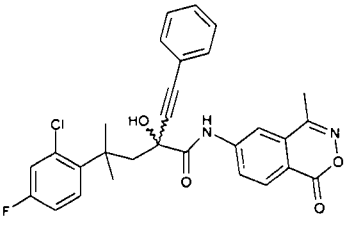
rac-6-{4-(2-cloro-4-fluorofenil)-2-hidroxi-2-[(4-metoxifenil)etinil]-4-metil pentanoilamino}-4-metil-2,3-benzoxazin-1-ona 12



La conversión de 4-metoxifenilacetileno (0,4 ml), nBuLi (0,6 ml, 1,6 M en hexano) y 6-[4-(2-cloro-4-fluorofenil)-4-metil-2-oxovaleroilamino]-4-metil-2,3-benzoxazin-1-ona (110 mg) a -78°C como se describió en el ejemplo 1 dio, después de cromatografía de columna con gel de sílice, los

compuestos del título en forma de sólido blanco (44 mg). ^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 1,63 (s, 3H, Me), 1,69 (s, 3H, Me), 2,91 - 3,01 (m, 3H), 3,81 (s, 3H, Me), 6,81 - 6,94 (m, 3H), 7,25 - 7,29 (m, 3H), 7,43 (dd, J = 8,4, 6,3 Hz, 1H), 7,58 (dd, J = 8,6, 2,3 Hz, 1H), 8,24 (d, J = 1,9 Hz, 1H), 8,31 (d, J = 8,6 Hz, 1H), 8,79 (br. s., 1H, NH). $C_{30}H_{26}ClFN_2O_5$ (549,0): LC-MS: m/z = 549 [M + H^+].

rac-6-{4-(2-cloro-4-fluorofenil)-2-hidroxi-4-metil-2-(feniletinil)pentanoilamino}-4-metil-2,3-benzoxazin-1-ona 13



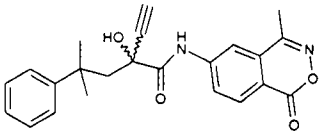
Se agregó fenilacetilida de litio (0,65 ml, 1M en THF) a 6-[4-(2-cloro-4-fluorofenil)-4-metil-2-oxovaleroilamino]-4-metil-2,3-benzoxazin-1-ona (136 mg) a -78°C y se agitó bajo argón a -78°C durante 2,5 h. Después de preparar como se describió en el ejemplo 1 y cromatografía de columna con gel de sílice y después de secar en la bomba de aceite, se obtuvo el compuesto del título en forma de espuma blanca, (102 mg).

^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 1,64 (s, 3H, Me), 1,70 (s, 3H, Me), 2,57 (s, 3H, Me), 2,92 - 3,03 (m, 3H), 6,82 - 6,86 (m, 1H), 6,91 - 6,93 (m, 1H), 7,30 - 7,36 (m, 5H), 7,44 (dd, J = 9,0, 6,2 Hz, 1H), 7,59 (dd, J = 8,6, 2,0 Hz, 1H), 8,23 (d, J

= 2,0 Hz, 1H), 8,31 (d, J = 8,2 Hz, 1H), 8,79 (br. s., NH); $C_{29}H_{24}ClFN_2O_4$ (519,0): HPLC-MS: m/z = 518 [M].

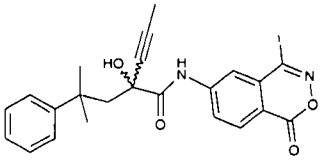
En forma análoga al ejemplo 10 se prepararon a partir de 6-(4-metilo-4-fenil-2-oxovaleroilamino)-4-metil-2,3-benzoxazin-1-ona y el halogenuro de alquinilmagnesio, los compuestos 14 y 15:

rac-6-[2-etinilo-2-hidroxi-4-metil-4-fenilpentanoilamino]-4-metil-2,3-benzoxazin-1-ona 14



^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 1,42 (3H), 1,59 (3H), 2,57 (3H), 2,64 (4H), 7,15 (1H), 7,31 (2H), 7,46 (2H), 7,58 (1H), 8,25 (1H), 8,30 (1H), 8,81 (1H).

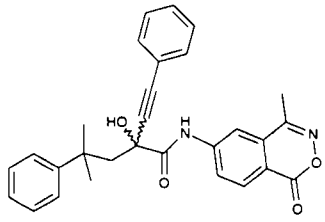
rac-6-[2-hidroxi-4-metil-4-fenil-2-propinilpentanoilamino]-4-metil-2,3-benzoxazin-1-ona 15



^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 1,42 (3H), 1,59 (3H), 2,50-2,65 (6H), 7,11 (1H), 7,30 (2H), 7,43 (2H), 7,58 (1H), 8,29 (2H), 8,85 (1H).

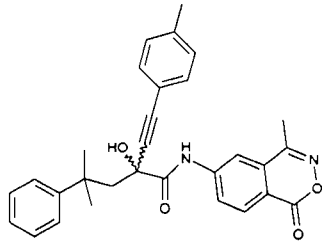
En forma análoga al ejemplo 1 se prepararon a partir de 6-(4-metilo-4-fenil-2-oxovaleroilamino)-4-metil-2,3-benzoxazin-1-ona y la respectiva arilacetilida de litio, los compuestos 15-28:

rac-6-[2-hidroxi-4-metil-4-fenil-2-(feniletinil)pentanoilamino]-4-metil-2,3-benzoxazin-1-ona 16



^{1}H-NMR (ppm, $CDCl_3$, 300 MHz): 1,47 (3H), 1,65 (3H), 2,57 (3H), 2,62-2,78 (3H), 7,15 (1H), 7,27-7,37 (5H), 7,40 (2H), 7,50 (2H), 7,59 (1H), 8,29 (2H), 8,90 (1H).

(+)-6-[2-hidroxi-4-metil-2-[(4-metilfenil)etinil]-4-fenilpentanoilamino]-4-metil-2,3-benzoxazin-1-ona 17a y (-)-6-[2-hidroxi-4-metil-2-[(4-metilfenil)etinil]-4-fenilpentanoilamino]-4-metil-2,3-benzoxazin-1-ona 17b

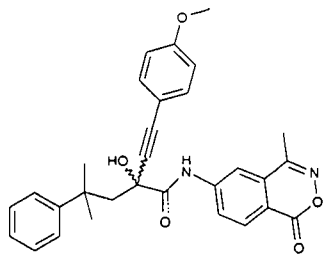


^{1}H-NMR (ppm, $CDCl_3$, 300 MHz): 1,48 (3H), 1,64 (3H), 2,36 (3H), 2,57 (3H), 2,60-2,80 (3H), 7,08-7,20 (3H), 7,30 (4H), 7,49 (2H), 7,60 (1H), 8,29 (2H), 8,90 (1H).

16a: $[\alpha]^D_{20}$: +28,4° ($CHCl_3$, 1,03 g/100 ml; γ=589 nm)

16b: $[\alpha]^D_{20}$: -28,6° ($CHCl_3$, 1,01 g/100 ml; γ=589 nm)

rac-6-[2-hidroxi-2-[(4-metoxfenil)etinil]-4-metil-4-fenilpentanoilamino]-4-metil-2,3-benzoxazin-1-ona 18



^{1}H-NMR (ppm, $CDCl_3$, 300 MHz): 1,47 (3H), 1,63 (3H), 2,56 (3H), 2,60-2,78 (3H), 3,80 (3H), 6,81 (2H), 7,13 (1H), 7,25-7,38 (4H), 7,48 (2H), 7,60 (1H), 8,28 (2H), 8,89 (1H).

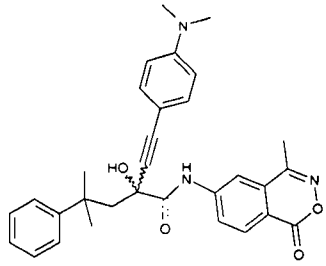
(+)-6-[2-hidroxi-2-[(4-metoxifenil)etinil]-4-metil-4-fenilpentanoilamino]-4-metil-2,3-benzoxazin-1-ona 18a y (-)-6-[2-hidroxi-2-[(4-metoxifenil)etinil]-4-metil-4-fenilpentanoilamino]-4-metil-2,3-benzoxazin-1-ona 18b

La mezcla racémica descrita en 18 fue separada por HPLC quiral preparativa (Columna Chiralpak AD 250x10 mm) para dar los enantiómeros 18a y 18b.

18a : $[\alpha]^D_{20}$: + 29,3° ($CHCl_3$, 1,12 g/100 ml; λ=589 nM)

18b : $[\alpha]^D_{20}$: - 30,0° ($CHCl_3$, 1,14 g/100 ml; λ=589 nM)

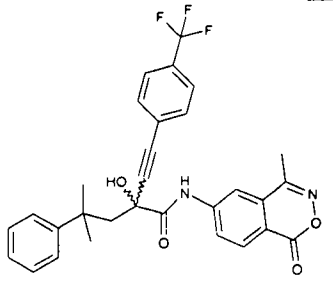
rac-6-[2-hidroxi-2-[(4-(N,N-dimetilamino)fenil)etinil]-4-metil-4-fenilpentanoilamino]-4-metil-2,3-benzoxazin-1-ona 19



^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 1,48 (3H), 1,62 (3H), 2,57 (3H), 2,60-2,75 (3H), 2,98 (6H), 6,58 (2H), 7,12 (1H), 7,23-

7,38 (4H), 7,48 (2H); 7,57 (1H), 8,28 (2H), 8,90 (1H).

rac-6-[2-hidroxi-4-metil-4-fenil-2-[(4-trifluorometilfenil)etinil]-pentanoilamino]-4-metil-2,3-benzoxazin-1-ona 20



^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 1,48 (3H), 1,63 (3H), 2,57 (3H), 2,64-2,80 (3H), 7,17 (1H), 7,33 (2H), 7,48 (4H), 7,56 (2H), 7,61 (1H), 8,30 (2H), 8,92 (1H).

(+)-6-[2-hidroxi-4-metil-4-fenil-2-[(4-trifluorometilfenil)etinil]-pentanoilamino]-4-metil-2,3-benzoxazin-1-ona 20a y

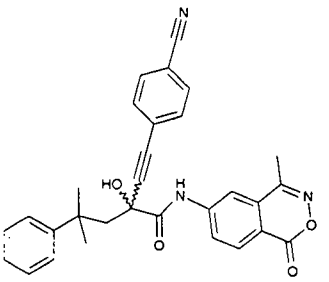
(-)-6-[2-hidroxi-4-metil-4-fenil-2-[(4-trifluorometilfenil)etinil]-pentanoilamino]-4-metil-2,3-benzoxazin-1-ona 20b

La mezcla racémica descrita en 20 fue separada por HPLC quiral preparativa (Columna Chiralpak AD 250x10 mm) para dar los enantiómeros 20a y 20b.

20a : $[\alpha]^{D}_{20}$: + 19,9° ($CHCl_3$, 1,05 g/100 ml; λ=589 nM)

20b : $[\alpha]^{D}_{20}$: - 20,4° ($CHCl_3$, 1,01 g/100 ml; λ=589 nM)

rac-6-[2-[(4-cianofenil)etinil]-2-hidroxi-4-metil-4-fenilpentanoilamino]-4-metil-2,3-benzoxazin-1-ona 21



^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 1,50 (3H), 1,62 (3H), 2,57 (3H), 2,63-2,82 (3H), 7,18 (1H), 7,35 (2H), 7,48 (4H), 7,55-7,68 (2H), 7,62 (1H), 8,30 (2H), 8,94 (1H).

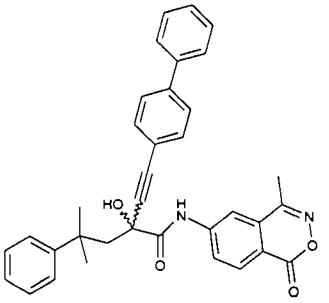
(+)-6-[2-[(4-cianofenil)etinil]-2-hidroxi-4-metil-4-fenilpentanoilamino]-4-metil-2,3-benzoxazin-1-ona 21a y (-)-6-[2-[(4-cianofenil)etinil]-2-hidroxi-4-metil-4-fenilpentanoilamino]-4-metil-2,3-benzoxazin-1-ona 21b

La mezcla racémica descrita en 21 fue separada por HPLC quiral preparativa (Columna Chiralpak AD 250x10 mm) para dar los enantiómeros 21a y 21b.

21a : $[\alpha]^{D}_{20}$: + 26,6° ($CHCl_3$, 1,12 g/100 ml; λ=589 nM)

21b : $[\alpha]^{D}_{20}$: - 26,8° ($CHCl_3$, 1,02 g/100 ml; λ=589 nM)

rac-6-[2-hidroxi-4-metil-4-fenil-2-[(4-fenilfenil)etinil]pentanoilamino]-4-metil-2,3-benzoxazin-1-ona 22



^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 1,50 (3H), 1,68 (3H), 2,58 (3H), 2,64-2,81 (3H), 7,18 (1H), 7,30-7,40 (3H), 7,41-7,61 (11H), 8,30 (2H), 8,92 (1H).

(+)-6-[2-hidroxi-4-metil-4-fenil-2-[(4-fenilfenil)etinil]pentanoilamino]-4-metil-2,3-benzoxazin-1-ona 22a y

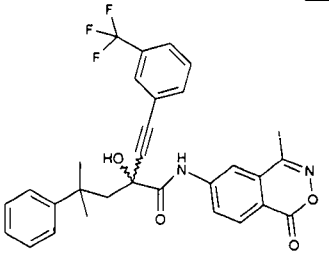
(-)-6-[2-hidroxi-4-metil-4-fenil-2-[(4-fenilfenil)etinil]pentanoilamino]-4-metil-2,3-benzoxazin-1-ona 22b

La mezcla racémica descrita en 22 fue separada por HPLC quiral preparativa (Columna Chiralpak AD 250x10 mm) para dar los enantiómeros 22a y 22b.

22a : $[\alpha]^D_{20}$: + 38,4° ($CHCl_3$, 1,06 g/100 ml; λ=589 nM)

22b : $[\alpha]^D_{20}$: - 30,6° ($CHCl_3$, 1,12 g/100 ml; λ=589 nM)

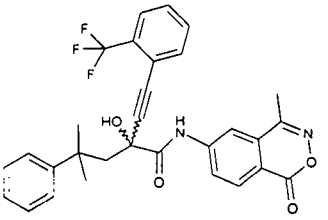
rac-6-[2-hidroxi-4-metil-4-fenil-2-[(3-trifluorometilfenil)etinil]-pentanoilamino]-4-metil-2,3-benzoxazin-1-ona 23



^{1}H-NMR (ppm, $CDCl_3$, 300 MHz): 1,52 (3H), 1,68 (3H), 2,60 (3H), 2,65-2,88 (3H), 7,21 (1H), 7,49 (2H), 7,42-7,70 (7H), 8,34 (2H), 8,96 (1H).

rac-6-[2-hidroxi-4-metil-4-fenil-2-[(2-trifluorometilfenil)etinil]-pentanoilamino]-4-metil-2,3-

benzoxazin-1-ona 24



^{1}H-NMR (ppm, $CDCl_3$, 600 MHz): 1,52 (3H), 1,65 (3H), 2,62 (3H), 2,69 (1H), 2,78 (1H), 2,91 (1H), 7,11 (1H), 7,32 (3H), 7,51 (3H), 7,57 (2H), 7,70 (1H), 8,20 (1H), 8,45 (1H), 8,75 (1H).

(+)-6-[2-hidroxi-4-metil-4-fenil-2-[(2-trifluorometilfenil)etinil]-pentanoilamino]-4-metil-2,3-benzoxazin-1-ona 24a y

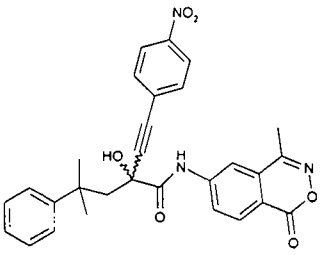
(-)-6-[2-hidroxi-4-metil-4-fenil-2-[(2-trifluorometilfenil)etinil]-pentanoilamino]-4-metil-2,3-benzoxazin-1-ona 24b

La mezcla racémica descrita en 24 fue separada por HPLC quiral preparativa (Columna Chiralpak AD 250x10 mm) para dar los enantiómeros 24a y 24b.

24a : $[\alpha]^{D}_{20}$: + 21,3° ($CHCl_3$, 1,00 g/100 ml; λ=589 nM)

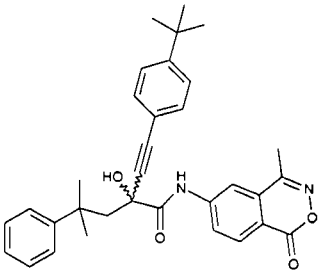
24b : $[\alpha]^{D}_{20}$: - 19,4° ($CHCl_3$, 1,00 g/100 ml; λ=589 nM)

rac-6-[2-hidroxi-4-metil-2-[(4-nitrofenil)etinil]-4-fenilpentanoilamino]-4-metil-2,3-benzoxazin-1-ona 25



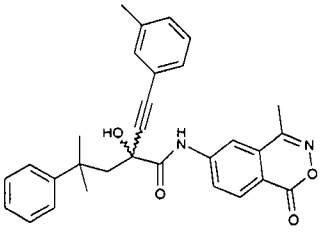
^{1}H-NMR (ppm, $CDCl_3$, 600 MHz): 1,47 (3H), 1,62 (3H), 2,55 (3H), 2,79 (1H), 2,81 (2H), 7,18 (1H), 7,34 (2H), 7,50 (4H), 7,63 (1H), 8,17 (2H), 8,80 (2H), 8,94 (1H).

rac-6-[2-[[4-(1,1-dimetiletil)fenil]etinil]-2-hidroxi-4-metil-4-fenilpentanoilamino]-4-metil-2,3-benzoxazin-1-ona 26



^{1}H-NMR (ppm, $CDCl_3$, 300 MHz): 1,32 (9H), 1,51 (3H), 1,68 (3H), 2,62 (3H), 2,65-2,82 (3H), 7,18 (1H), 7,30-7,40 (6H), 7,52 (2H), 7,63 (1H), 8,32 (2H), 8,93 (1H).

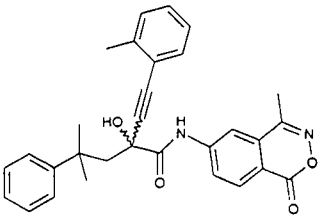
rac-6-[2-hidroxi-4-metil-2-[(3-metilfenil)etinil]-4-fenilpentanoilamino]-4-metil-2,3-benzoxazin-1-ona 27



^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 1,47 (3H), 1,63 (3H), 2,30

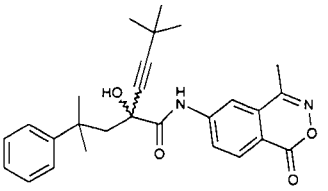
(3H), 2,58 (3H), 2,62-2,80 (3H), 7,12-7,26 (5H), 7,32 (2H), 7,50 (2H), 7,60 (1H), 8,30 (2H), 8,90 (1H).

rac-6-[2-hidroxi-4-metil-2-[(2-metilfenil)etinil]-4-fenilpentanoilamino]-4-metil-2,3-benzoxazin-1-ona 28



^{1}H-NMR (ppm, $CDCl_3$, 300 MHz): 1,47 (3H), 1,65 (3H), 2,38 (3H), 2,58 (3H), 2,62-2,80 (3H), 7,08-7,42 (7H), 7,49 (2H), 7,60 (1H), 8,22-8,36 (2H), 8,90 (1H).

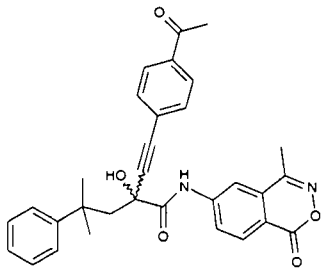
rac-6-[2-(3,3-dimetilbutinilo)-2-hidroxi-4-metil-4-fenilpentanoilamino]-4-metil-2,3-benzoxazin-1-ona 29



^{1}H-NMR (ppm, $CDCl_3$, 300 MHz): 1,20 (9H), 1,43 (3H), 1,60 (3H), 2,46 (1H), 2,50-2,63 (5H), 7,11 (1H), 7,28 (2H), 7,43 (2H), 7,54 (1H), 8,22 (1H), 8,29 (1H), 8,32 (1H).

En forma análoga al ejemplo 7 se preparó, a partir del compuesto descrito en 13 y 4'-yodacetofenona, el siguiente compuesto:

rac-6-[2-[(4-acetilfenil)etinil]-2-hidroxi-4-metil-4-fenilpentanoilamino]-4-metil-2,3-benzoxazin-1-ona 30



^{1}H-NMR (ppm, $CDCl_3$, 300 MHz): 1,48 (3H), 1,63 (3H), 2,56 (3H), 2,60 (3H), 2,63-2,82 (3H), 7,18 (1H), 7,33 (2H), 7,40-7,56 (4H), 7,62 (1H), 7,90 (2H), 8,30 (2H), 8,93 (1H).

(+)-6-[2-[(4-acetilfenil)etinil]-2-hidroxi-4-metil-4-fenilpentanoilamino]-4-metil-2,3-benzoxazin-1-ona 30a y (-)-6-[2-[(4-acetilfenil)etinil]-2-hidroxi-4-metil-4-fenilpentanoilamino]-4-metil-2,3-benzoxazin-1-ona 30b

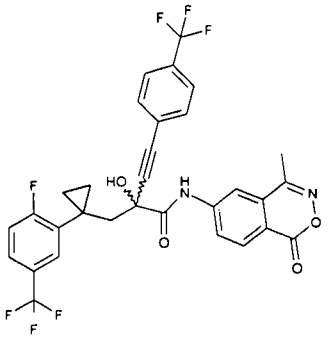
La mezcla racémica descrita en 30 fue separada por HPLC quiral preparativa (Columna Chiralpak AD 250x10 mm) para dar los enantiómeros 30a y 30b.

30a : $[\alpha]^{D}_{20}$: + 31,3° ($CHCl_3$, 1,09 g/100 ml; λ=589 nM)

30b : $[\alpha]^{D}_{20}$: - 28,4° ($CHCl_3$, 1,09 g/100 ml; λ=589 nM)

En forma análoga al ejemplo 1 se prepararon, a partir de 6-[3-[1-(2-flúor-5-trifluorometilfenil)ciclopropil]-2-oxopropionilamino]-4-metil-2,3-benzoxazin-1-ona, los compuestos 30 y 31.

rac-6-[2-[(2-flúor-5-trifluorometilfenil)ciclopropilmetil]-2-hidroxi-4-(4-trifluorometilfenil)but-3-inaoilamino]-4-metil-2,3-benzoxazin-1-ona 31



^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 0,90 (1H), 1,00-1,15 (3H), 2,51 (1H), 2,55 (3H), 2,68 (1H), 3,18 (1H), 7,01 (1H), 7,30 (1H), 7,41 (2H), 7,56 (2H), 7,63 (1H), 7,68 (1H), 8,19 (1H), 8,31 (1H), 8,98 (1H).

(+)-6-[2-[(2-flúor-5-trifluorometilfenil)ciclopropilmetil]-2-hidroxi-4-(4-trifluorometilfenil)but-3-inaoilamino]-4-metil-2,3-benzoxazin-1-ona 31a y

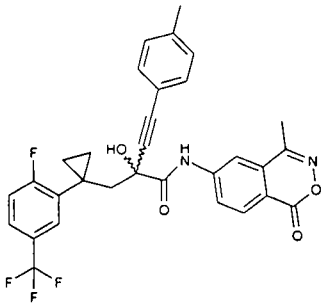
(-)-6-[2-[(2-flúor-5-trifluorometilfenil)ciclopropilmetil]-2-hidroxi-4-(4-trifluorometilfenil)but-3-inaoilamino]-4-metil-2,3-benzoxazoin-1-ona 31b

La mezcla racémica descrita en 31 fue separada por HPLC quiral preparativa (Columna Chiralpak AD 250x10 mm) para dar los enantiómeros 31a y 31b.

31a : $[\alpha]^{D}_{20}$: + 2,3° ($CHCl_3$, 1,00 g/100 ml; λ=589 nM)

31b : $[\alpha]^{D}_{20}$: - 1,9° ($CHCl_3$, 1,00 g/100 ml; λ=589 nM)

rac-6-[2-[(2-flúor-5-trifluorometilfenil)ciclopropilmetil]-2-hidroxi-4-(4-metilfenil)but-3-inaoilamino]-4-metil-2,3-benzoxazin-1-ona 32



^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 0,88 (1H), 0,98-1,13 (3H), 2,34 (3H), 2,44 (1H), 2,55 (3H), 2,70 (1H), 3,02 (1H), 7,01 (1H), 7,10 (2H), 7,22 (2H), 7,30 (1H), 7,64 (2H), 8,19 (1H), 8,31 (1H), 8,98 (1H).

(+)-6-[2-[(2-flúor-5-trifluorometilfenil)ciclopropilmetil]-2-hidroxi-4-(4-metilfenil)but-3-inaoilamino]-4-metil-2,3-benzoxazin-1-ona 32a y

(-)-6-[2-[(2-flúor-5-trifluorometilfenil)ciclopropilmetil]-2-hidroxi-4-(4-metilfenil)but-3-inaoilamino]-4-metil-2,3-benzoxazin-1-ona 32b

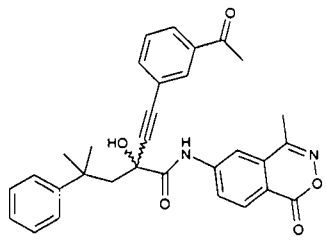
La mezcla racémica descrita en 32 fue separada por HPLC quiral preparativa (Columna Chiralpak AD 250x10 mm) para dar los enantiómeros 32a y 32b.

32a : $[\alpha]^{D}_{20}$: + 8,6° ($CHCl_3$, 1,00 g/100 ml; λ=589 nM)

32b : $[\alpha]^{D}_{20}$: - 8,7° ($CHCl_3$, 1,00 g/100 ml; λ=589 nM)

En forma análoga al ejemplo 7 y a partir del compuesto descrito en 14 y 3'-yodacetofenona se preparó el siguiente compuesto.

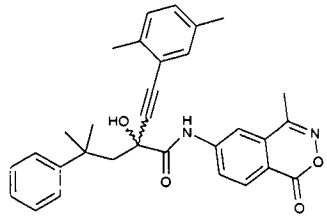
rac-6-[2-[(3-acetilfenil)etinil]-2-hidroxi-4-metil-4-fenilpentanoilamino]-4-metil-2,3-benzoxazin-1-ona 33



^{1}H-NMR (ppm, $CDCl_3$, 300 MHz): 1,49 (3H), 1,63 (3H), 2,57 (6H), 2,62-2,81 (3H), 7,16 81H), 7,28-7,70 (7H), 7,90-8,00 (2H), 8,30 (2H), 8,94 (1H).

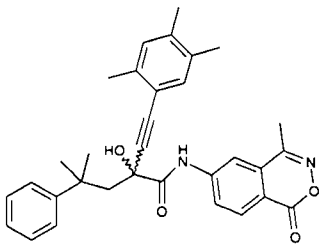
En forma análoga al ejemplo 1 se prepararon, a partir de 6-(4-metilo-4-fenil-2-oxovaleroilamino)-4-metil-2,3-benzoxazin-1-ona y la respectiva arilacetilida de litio, los compuestos 34 y 35:

rac-6-[2-[(2,5-dimetilfenil)etinil]-2-hidroxi-4-metil-4-fenilpentanoilamino]-4-metil-2,3-benzoxazin-1-ona <u>34</u>



^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 1,49 (3H), 1,62 (3H), 2,27 (3H), 2,33 (3H), 2,57 (3H), 2,65-2,78 (3H), 7,03 (2H), 7,13 (2H), 7,30 (2H), 7,50 (2H), 7,61 (1H), 8,22 (1H), 8,30 (1H), 8,89 (1H).

rac-6-[2-[(2,4,5-trimetilfenil)etinil]-2-hidroxi-4-metil-4-fenilpentanoilamino]-4-metil-2,3-benzoxazin-1-ona <u>35</u>



^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 1,47 (3H), 1,64 (3H), 2,18 (3H), 2,21 (3H), 2,30 (3H), 2,56 (3H), 2,65-2,77 (3H), 6,93 (1H), 7,12 (2H), 7,30 (2H), 7,48 (2H), 7,59 (1H), 8,22 (1H), 8,29 (1H), 8,90 (1H).

(+)-6-[2-[(2,4,5-trimetilfenil)etinil]-2-hidroxi-4-metil-4-fenilpentanoilamino]-4-metil-2,3-benzoxazin-1-ona 35a y (-)-6-[2-[(2,4,5-trimetilfenil)etinil]-2-hidroxi-4-metil-4-fenilpentanoilamino]-4-metil-2,3-benzoxazin-1-ona 35b

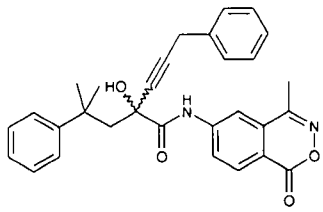
La mezcla racémica descrita en 35 fue separada por HPLC quiral preparativa (Columna Chiralpak AD 250x10 mm) para dar los enantiómeros 35a y 35b.

35a : $[\alpha]^D_{20}$: + 30,6° ($CHCl_3$, 0,97 g/100 ml; λ=589 nM)

35b : $[\alpha]^D_{20}$: - 28,0° ($CHCl_3$, 0,96 g/100 ml; λ=589 nM)

En forma análoga al ejemplo 9 se preparó, a partir de 3-fenilo-1-propina, nBuLi y 6-(4-metilo-4-fenil-2-oxovaleroilamino)-4-metil-2,3-benzoxazin-1-ona, el siguiente compuesto:

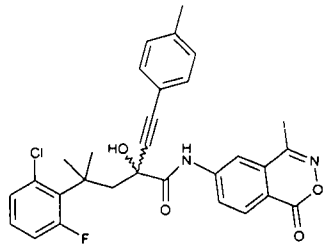
rac-6-{2-(2-fenil)-2-metilpropil]-2-hidroxi-5-fenilpent-3-inaoilamino}-4-metil-2,3-benzoxazin-1-ona 36



^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 1,42 (3H), 1,53 (3H), 2,55-2,70 (6H), 3,58 (2H), 7,11 (1H), 7,20-7,35 (7H), 7,41 (2H), 7,48 (1H), 8,20 (1H), 8,28 (1H), 8,80 (1H).

En forma análoga al ejemplo 1 y a partir de 6-(4-metilo-4-(2-cloro-6-fluorofenil)-2-oxovaleroilamino)-4-metil-2,3-benzoxazin-1-ona y la respectiva arilacetilida de litio, se prepararon los compuestos 37 y 38:

rac-6-[2-hidroxi-4-metil-4-(2-cloro-6-fluorofenil)-2-(4-metilfenil-etinil)pentanoilamino]-4-metil-2,3-benzoxazin-1-ona 37



^{1}H-NMR (ppm, $CDCl_3$, 300 MHz): 1,73 (3H), 1,82 (3H), 2,33 (3H), 2,57 (3H), 2,88-3,02 (3H), 6,75-6,96 (2H), 7,01 (1H), 7,09 (2H), 7,27 (2H), 7,60 (1H), 8,22-8,35 (2H), 8,96 (1H).

(+)-6-[2-hidroxi-4-metil-4-(2-cloro-6-fluorofenil)-2-(4-metilfenil-etinil)pentanoilamino]-4-metil-2,3-benzoxazin-1-ona 37a y

(-)-6-[2-hidroxi-4-metil-4-(2-cloro-6-fluorofenil)-2-(4-

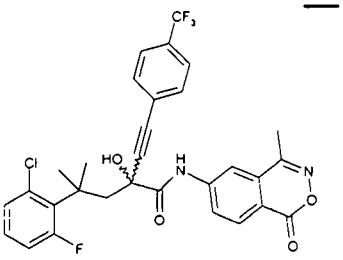
metilfenil-etinil)pentanoilamino]-4-metil-2,3-benzoxazin-1-ona 37b

La mezcla racémica descrita en 37 fue separada por HPLC quiral preparativa (Columna Chiralpak AD 250x10 mm) para dar los enantiómeros 37a y 37b.

37a : $[\alpha]^{D}_{20}$: + 21,5° ($CHCl_3$, 1,00 g/100 ml; λ=589 nM)

37b : $[\alpha]^{D}_{20}$: - 21,0° ($CHCl_3$, 1,04 g/100 ml; λ=589 nM)

rac-6-[2-hidroxi-4-metil-4-(2-cloro-6-fluorofenil)-2-(4-(trifluorometil)fenil-etinil)pentanoilamino]-4-metil-2,3-benzoxazin-1-ona 38



^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 1,60 (3H), 1,93 (3H), 2,36 (1H), 2,56-2,72 (5H), 7,04 (1H), 7,14 (2H), 7,45 (2H), 7,53 (2H), 7,80 (1H), 8,35-8,45 (2H), 8,90 (1H).

(+)-6-[2-hidroxi-4-metil-4-(2-cloro-6-fluorofenil)-2-(4-(trifluorometil)fenil-etinil)pentanoilamino]-4-metil-2,3-benzoxazin-1-ona 38a y

(-)-6-[2-hidroxi-4-metil-4-(2-cloro-6-fluorofenil)-2-(4-(trifluorometil)fenil-etinil)pentanoilamino]-4-metil-2,3-benzoxazin-1-ona 38b

La mezcla racémica descrita en 38 fue separada por HPLC quiral preparativa (Columna Chiralpak AD 250x10 mm) para dar

los enantiómeros 38a y 38b.

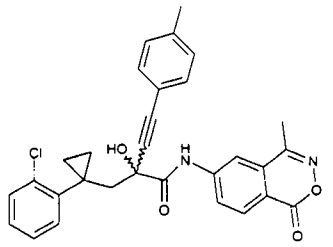
38a : $[\alpha]^{D}_{20}$: + 143,2° ($CHCl_3$, 1,05 g/100 ml; λ=589 nM)

38b : $[\alpha]^{D}_{20}$: - 137,8° ($CHCl_3$, 1,12 g/100 ml; λ=589 nM)

En forma análoga al ejemplo 1 y a partir de 6-(4-metilo-4-(2-clorofenil)-2-oxovaleroilamino)-4-metil-2,3-benzoxazin-1-ona y la respectiva arilacetilida de litio se prepararon los compuestos 39 y 40:

rac-6-[2-(2-clorofenil)ciclopropilmetil]-2-hidroxi-4-(4-metilfenil)but-3-inaoilamino]-4-metil-2,3-benzoxazin-1-ona

39



^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 0,84 (1H), 1,00 (1H), 1,08-1,22 (2H), 2,36 (3H), 2,53 (3H), 2,90 (1H), 7,03-7,18 (4H), 7,23-7,38 (3H), 7,50 (1H), 7,60 (1H), 8,22 (1H), 8,29 (1H), 8,91 (1H).

(+)-6-[2-(2-clorofenil)ciclopropilmetil]-2-hidroxi-4-(4-metilfenil)but-3-inaoilamino]-4-metil-2,3-benzoxazin-1-ona

39a y

(-)-6-[2-(2-clorofenil)ciclopropilmetil]-2-hidroxi-4-(4-metilfenil)but-3-inaoilamino]-4-metil-2,3-benzoxazin-1-ona

39b

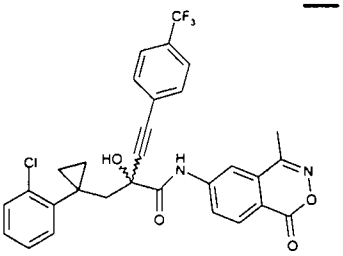
La mezcla racémica descrita en 39 fue separada por HPLC

quiral preparativa (Columna Chiralpak AD 250x10 mm) para dar los enantiómeros 39a y 39b.

39a : $[\alpha]^{D}_{20}$: + 30,8° ($CHCl_3$, 1,00 g/100 ml; λ=589 nM)

39b : $[\alpha]^{D}_{20}$: - 28,3° ($CHCl_3$, 1,00 g/100 ml; λ=589 nM)

rac-6-[2-(2-clorofenil)ciclopropilmetil]-2-hidroxi-4-(4-trifluoro-metilfenil)but-3-inaoilamino]-4-metil-2,3-benzoxazin-1-ona 40



^{1}H-NMR (ppm, $CDCl_3$, 300 MHz): 0,91 (1H), 1,02 (1H), 1,08-1,25 (2H), 2,53 (3H), 3,00 (1H), 7,02-7,18 (2H), 7,28 (1H), 7,42-7,54 (3H), 7,55-7,67 (3H), 8,22 (1H), 8,32 (1H), 8,91 (1H).

(+)-6-[2-(2-clorofenil)ciclopropilmetil]-2-hidroxi-4-(4-trifluoro-metilfenil)but-3-inaoilamino]-4-metil-2,3-benzoxazin-1-ona 40a y

(-)-6-[2-(2-clorofenil)ciclopropilmetil]-2-hidroxi-4-(4-trifluoro-metilfenil)but-3-inaoilamino]-4-metil-2,3-benzoxazin-1-ona 40b

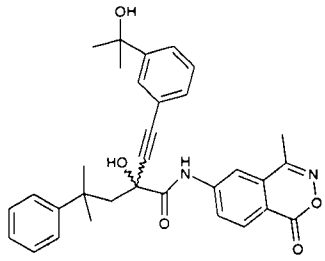
La mezcla racémica descrita en 40 fue separada por HPLC quiral preparativa (Columna Chiralpak AD 250x10 mm) para dar los enantiómeros 40a y 40b.

40a : $[\alpha]^{D}_{20}$: + 20,9° ($CHCl_3$, 1,06 g/100 ml; λ=589 nM)

40b : $[\alpha]^{D}_{20}$: - 20,6° ($CHCl_3$, 1,05 g/100 ml; λ=589 nM)

rac-6-[2-[[3-(1-hidroxi-1-metiletil)fenil]etinil]-2-hidroxi-4-metil-

4-fenilpentanoilamino]-4-metil-2,3-benzoxazin-1-ona 41



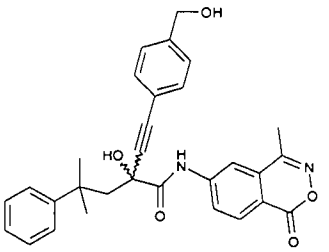
Se diluyen 59 µl de una solución 3 molar de cloruro de metilmagnesio en 1 ml tetrahidrofurano absoluto. Se enfría a -70°C y luego se adiciona una solución de 30 mg del compuesto descrito en el ejemplo 33 en 0,5 ml tetrahidrofurano absoluto. Se sigue agitando 2,5 horas a -70°C y se vierte la mezcla de reacción sobre solución acuosa saturada de cloruro de amonio. Se extrae con acetato de etilo. Las fases orgánicas reunidas se lavan con solución saturada de cloruro de sodio y se secan sobre sulfato de sodio. Después de cromatografía de columna con gel de sílice se obtienen 16 mg del producto.

^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 1,46 (3H), 1,53 (6H), 1,62 (3H), 1,80 (1H), 2,55 (3H), 2,65-2,90 (3H), 7,12 (1H), 7,30 (3H), 7,40-7,52 (3H), 7,53 (1H), 7,60 (1H), 8,27 (2H), 8,95 (1H).

En forma análoga al ejemplo 7 se preparó, a partir del

compuesto descrito en el ejemplo 14 y 4-yodobencilalcohol, el siguiente compuesto:

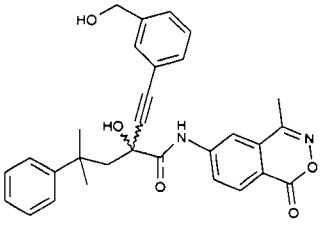
rac-6-[2-[[4-(hidroximetil)fenil]etinil]-2-hidroxi-4-metil-4-fenilpentanoilamino]-4-metil-2,3-benzoxazin-1-ona 42



^{1}H-NMR (ppm, $CDCl_3$, 300 MHz): 1,47 (3H), 1,60 (3H), 1,80 (1H), 2,57 (3H), 2,62-2,83 (3H), 4,68 (2H), 7,13 (1H), 7,25-7,43 (6H), 7,48 (2H), 7,59 (1H), 8,25-8,32 (2H), 8,91 (1H).

En forma análoga al ejemplo 7 se preparó, a partir del compuesto descrito en el ejemplo 14 y 3-yodobencilalcohol, el siguiente compuesto:

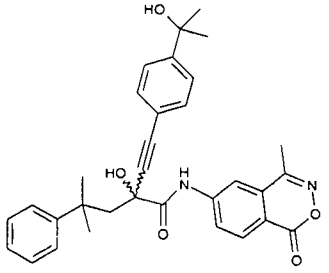
rac-6-[2-[[3-(hidroximetil)fenil]etinil]-2-hidroxi-4-metil-4-fenilpentanoilamino]-4-metil-2,3-benzoxazin-1-ona 43



^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 1,48 (3H), 1,62 (3H), 1,79 (1H), 2,57 (3H), 2,62-2,80 (3H), 4,68 (2H), 7,15 (1H), 7,25-7,39 (5H), 7,40 (1H), 7,49 (2H), 7,60 (1H), 8,29 (2H), 8,91 (1H).

En forma análoga al ejemplo 41 se preparó, a partir del compuesto descrito en el ejemplo 30 y solución de cloruro de metilmagnesio, el siguiente compuesto:

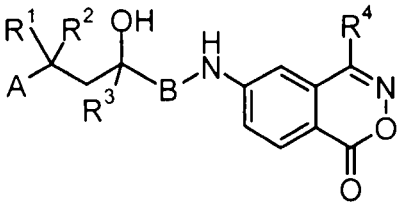
rac-6-[2-[[4-(1-hidroxi-1-metiletil)fenil]etinil]-2-hidroxi-4-metil-4-fenilpentanoilamino]-4-metil-2,3-benzoxazin-1-ona 44



^{1}H-NMR (ppm, $CDCl_3$, 400 MHz): 1,47 (3H), 1,55 (6H), 1,62 (3H), 1,70 (1H), 2,55 (3H), 2,60-2,80 (3H), 7,14 (1H), 7,28-7,40 (4H), 7,41 (2H), 7,48 (2H), 7,60 (1H), 8,25-8,32 (2H), 8,90 (1H).

REIVINDICACIONES

1. Loc compuestos de la fórmula general I



donde

R^1 y R^2 representan independientemente uno de otro, un átomo de hidrógeno, un grupo C_1-C_5-alquilo lineal o no-lineal, ramificado o no-ramificado, además, junto con el átomo de C de la cadena forman un anillo con un total de 3-7 miembros

R^3 representa un radical C≡C-R^a, donde

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

K significa ciano, halógeno, hidroxilo, 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 es C_3-C_{10}-cicloalquilo, heterocicloalquilo, opcionalmente mono o polisustituido con M, de manera igual o diferente o significa arilo o heteroarilo,

opcionalmente mono o polisustituido con L,

L significa C_1-C_8-alquilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, C_1-C_6-perfluoralquilo, C_1-C_6-perfluoralcoxilo, C_1-C_6-alcoxi-C_1-C_6-alcoxilo, $(CH_2)_p$-C_3-C_{10}-cicloalquilo, $(CH_2)_p$-heterocicloalquilo, $(CH_2)_pCN$, $(CH_2)_pHal$, $(CH_2)_pNO_2$, $(CH_2)_p$-C_6-C_{12}-arilo, $(CH_2)_p$-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 $-(CH_2)_{n+2}-$, donde n=1 o 2 y los átomos de oxigeno y/o carbono en posición final están unidos con átomos de carbono del anillo directamente adyacentes,

M es C_1-C_6-alquilo o un grupo $-COR^b$, CO_2R^b, $-O-$

R^b, o $-NR^cR^d$, donde

R^b significa un hidrógeno o un grupo C_1-C_6-alquilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, C_3-C_{10}-cicloalquilo, C_6-C_{12}-arilo o C_1-C_3-perfluoralquilo y

R^c y R^d representan independientemente uno de otro un hidrógeno, C_1-C_6-alquilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, C_3-C_{10}-cicloalquilo, C_6-C_{12}-arilo, $C(O)R^b$ o un grupo hidroxilo, donde cuando

R^c es un grupo hidroxilo, R^d solamente puede ser un hidrógeno, un C_1-C_6-alquilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, C_3-C_{10}-cicloalquilo o C_6-C_{12}-arilo y viceversa, y

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

p puede ser un número de 0- 6,

o

R^3 representa un radical $C=C-R^gR^h$, donde

R^g y R^h representan independientemente uno de otro un hidrógeno o un C_1-C_8-alquilo, C_2-C_8-alquenilo o C_2-C_8-alquinilo, opcionalmente mono o polisustituido con X, de manera igual o diferente, donde

X es un ciano, halógeno, hidroxilo, nitro,

$-C(O)R^b$, CO_2R^b, $-O-R^b$, $-C(O)-NR^cR^d$, NR^cR^d con los significados mencionados más arriba para R^b, R^c y R^d y

R^4 es un átomo de hidrógeno, un grupo metilo o etilo o un grupo C_1-C_3-alquilo parcial o totalmente fluorado

A representa un anillo aromático mono- o bicíclico, carbocíclico o heterocíclico, que puede estar opcionalmente mono- o polisustituido con C_1-C_8-alquilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, C_1-C_6-perfluoralquilo, C_1-C_6-perfluoralcoxilo, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alcoxilo, $(CH_2)_p$-C_3-C_{10}-cicloalquilo, $(CH_2)_p$-heterocicloalquilo, $(CH_2)_pCN$, $(CH_2)_pHal$, $(CH_2)_pNO_2$, $(CH_2)_p$-C_6-C_{12}-arilo, $(CH_2)_p$-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 $-(CH_2)_{n+2}-$, donde n=1 o 2 y los átomos de oxigeno y/o carbono en posición final

están unidos con átomos de carbono del anillo directamente adyacentes, o

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

o

A representa un grupo alquenilo $-CR^5=CR^6R^7$, donde R^5, R^6 y R^7 son iguales o diferentes y representan independientemente uno de otro, átomos de hidrógeno, átomos de halógeno, radicales arilo o un grupo C_1-C_5-alquilo insustituido o parcial o completamente fluorado o

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

B representa un grupo carbonilo o CH_2,

así como sus sales aceptables para uso farmacéutico.

2 Los compuestos de acuerdo con la reivindicación 1, e los cuales R^1 y R^2 representan preferentemente un átomo de hidrógeno, un metilo- o un grupo etilo.

3. Los compuestos de acuerdo con la reivindicación 1, en los cuales R^1 y R^2 preferentemente forman un anillo junto con el átomo de C de la cadena, con un total de 3-7 miembros.

4. Los compuestos de acuerdo con las reivindicaciones 1 a 3, en los cuales R^3 representa preferentemente alquenilo, alquinilo, arilalquinilo, heteroarilalquinilo cicloalquilalquinilo

heterocicloalquilalquinilo.

5. Los compuestos de acuerdo con cualquiera de las reivindicaciones anteriores, en los cuales R^3 representa preferentemente un grupo vinilo, etinilo, propinilo, butinilo, pentinilo, hexinilo, heptinilo, octinilo, hidroxilpropinilo, 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. Los compuestos de acuerdo con cualqueira de las reivindicaciones anteriores, en los cuales A es preferentemente un anillo aromático.

7. Los compuestos de acuerdo con cualquiera de las reivindicaciones anteriores, en los cuales A es preferentemente un radical fenilo o naftilo.

8. Compuestos de acuerdo con la reivindicación 7, en los cuales A es preferentemente un radical fenilo insustituido u opcionalmente mono o polisustituido.

9. Compuestos de acuerdo con la reivindicación 8, en los cuales el radical fenilo está sustituido

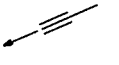
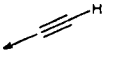
preferentemente por uno o dos átomos de halógeno o un grupo trifluorometilo.

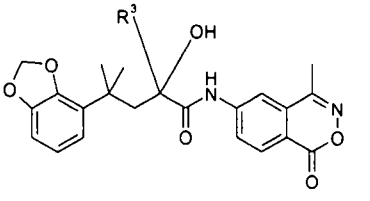
10. Compuestos de acuerdo con la reivindicación 9, en los cuales los átomos de halógeno son preferentemente cloro y/o flúor.

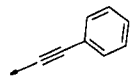
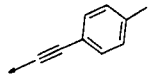
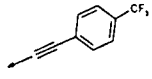
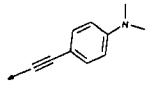
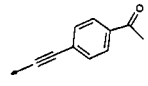
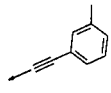
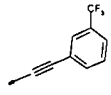
11. Compuestos de acuerdo con las reivindicaciones 1-8, en los cuales A es preferentemente un anillo fenilo sustituido con $-O-(CH_2)_n-O-$ o $-O-(CH_2)_n-CH_2-$, donde los respectivos átomos de C del anillo directamente adyacentes están unidos.

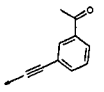
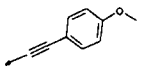
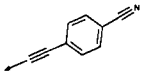
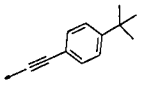
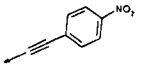
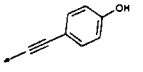
12. Los compuestos de acuerdo con cualquiera de las reivindicaciones anteriores, en los cuales R^4 es un átomo de hidrógeno, un radical metilo- o trifluorometilo.

13. Compuestos de acuerdo con las reivindicaciones 1 a 5, en los cuales son las siguientes:

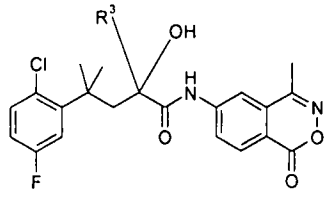
°	Racémico o Enantiómero	R3
1	Rac	
2	-	
3	+	
4	Rac	
5	+	
6	-	
7	Rac	

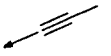
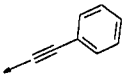
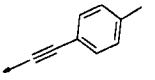
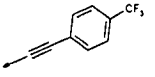
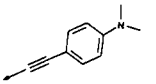
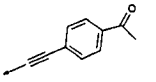
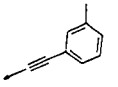


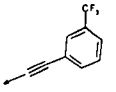
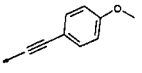
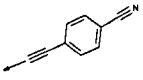
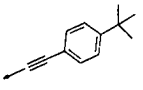
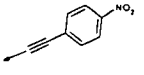
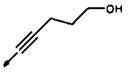
8	+	
9	-	
10	Rac	
11	+	
12	-	
13	Rac	
14	+	
15	-	
16	Rac	
17	+	
18	-	
19	Rac	
20	+	
21	-	
22	Rac	
23	+	
24	-	
25	Rac	
26	+	
27	-	
28	Rac	
29	+	
30	-	
31	Rac	
32	+	

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	-	

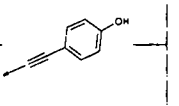
N°	Racémico o enantiómero	R3
52	Rac	
53	-	
54	+	

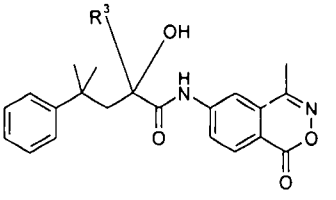


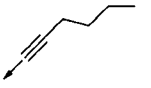
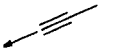
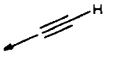
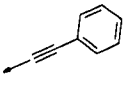
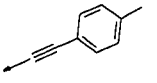
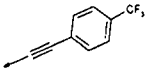
55	Rac	
56	+	
57	-	
58	Rac	
59	+	
60	-	
61	Rac	
62	+	
63	-	
64	Rac	
65	+	
66	-	
67	Rac	
68	+	
69	-	
70	Rac	
71	+	
72	-	
73	Rac	
74	+	
75	-	
76	Rac	
77	+	
78	-	

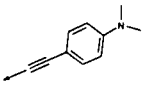
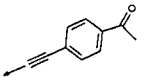
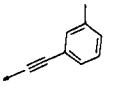
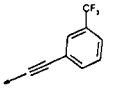
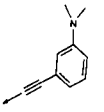
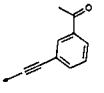
79	Rac	
80	+	
81	-	
82	Rac	
83	+	
84	-	
85	Rac	
86	+	
87	-	
88	Rac	
89	+	
90	-	
91	Rac	
92	+	
93	-	
94	Rac	
95	+	
96	-	
97	Rac	
98	+	
99	-	
100	Rac	
191	+	
102	-	

350

103	Rac	
104	+	
105	-	



N°	Racémico o enantiómero	R3
106	Rac	
107	-	
108	+	
109	Rac	
110	+	
111	-	
112	Rac	
113	+	
114	-	
115	Rac	
116	+	
117	-	
118	Rac	
119	+	
120	-	
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	
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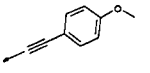
142	rac	
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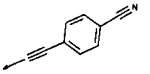
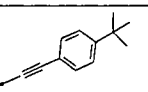
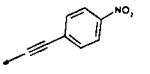
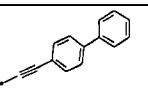
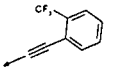
144	-	
145	rac	
146	+	
147	-	

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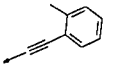
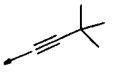
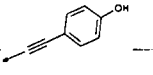
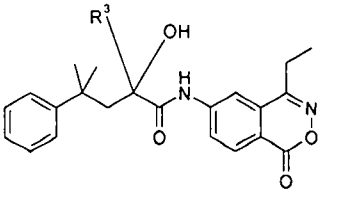
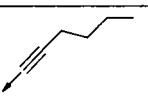
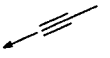
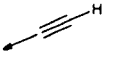
159	-	
160	rac	
161	+	
162	-	
163	rac	
164	+	
165	-	
166	rac	
167	+	
168	-	

N°	Racémico o enantiómero	R3



169	rac	
170	-	
171	+	
172	rac	
173	+	
174	-	
175	rac	
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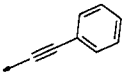
177	-	
178	rac	
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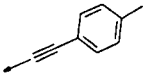
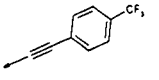
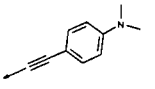
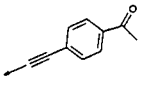
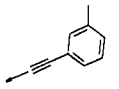
180	-	
181	rac	
182	+	
183	-	
184	rac	
185	+	
186	-	
187	rac	
188	+	
189	-	
190	rac	
191	+	
192	-	

193	rac	
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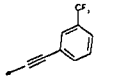
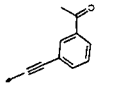
195	-	
196	rac	
197	+	
198	-	
199	rac	
200	+	
201	-	
202	rac	
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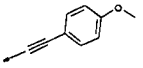
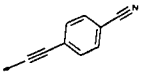
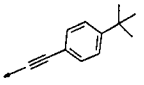
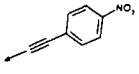
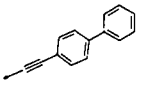
204	-	
205	rac	
206	+	
207	-	
208	rac	
209	+	
210	-	
211	rac	
212	+	
213	-	
214	rac	
215	+	
216	-	

217	rac	
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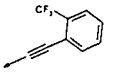
220	rac	
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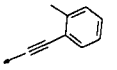
222	-	
223	rac	
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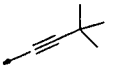
226	rac	
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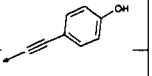
229	rac	
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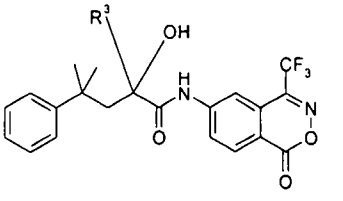
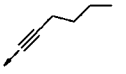
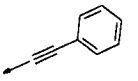
231	-	



N°	Racémico o enantiómero	R3
232	rac	
233	-	
234	+	
235	rac	
236	+	
237	-	

238	rac	
239	+	
240	-	
241	rac	
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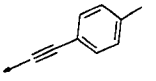
244	rac	
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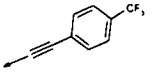
247	rac	
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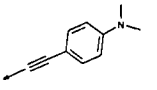
250	rac	
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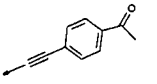
252	-	
253	rac	
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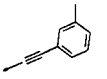
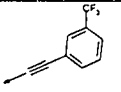
256	rac	
257	+	
258	-	
259	rac	
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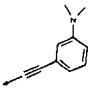
262	rac	

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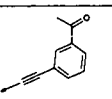
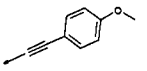
264	-	
265	rac	
266	+	
267	-	
268	rac	
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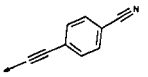
270	-	
271	rac	
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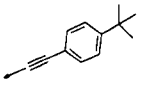
273	-	
274	rac	
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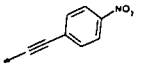
276	-	
277	rac	
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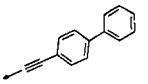
280	rac	
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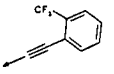
282	-	
283	rac	
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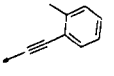
286	rac	

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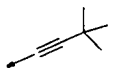
289	rac	
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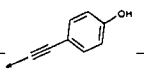
291	-	
292	rac	
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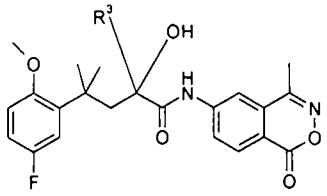
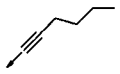
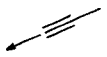
294	-	



N°	Racémico o enantiómero	R3
295	rac	
296	-	
297	+	
298	rac	
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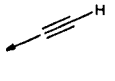
300	-	
301	rac	
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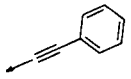
303	-	
304	rac	
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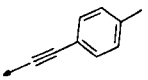
306	-	
307	rac	
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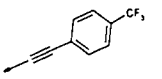
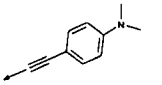
309	-	
310	rac	
311	+	
312	-	
313	rac	
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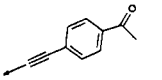
315	-	
316	rac	
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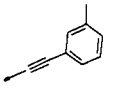
317	-	
319	rac	
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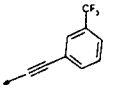
322	rac	
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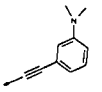
325	rac	
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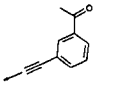
328	rac	
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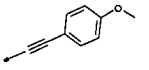
331	rac	
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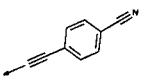
333	-	

334	rac	
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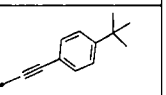
337	rac	
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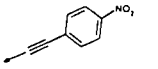
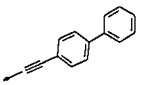
340	rac	
341	+	
342	-	
343	rac	
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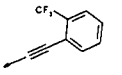
346	rac	
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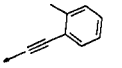
348	-	
349	rac	
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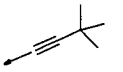
351	-	
352	rac	
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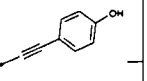
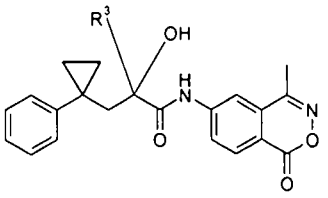
355	rac	
356	+	
357	-	



Nº	Racémico o enantiómero	R3
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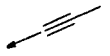
359	-	
360	+	
361	rac	
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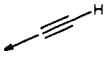
364	rac	
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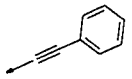
367	rac	
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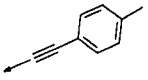
370	rac	
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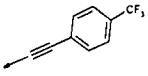
373	rac	
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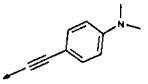
376	rac	
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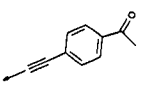
379	rac	

360

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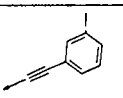
382	rac	
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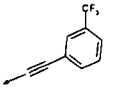
385	rac	
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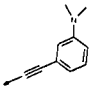
388	rac	
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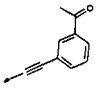
391	rac	
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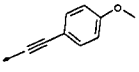
394	rac	
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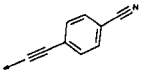
397	rac	
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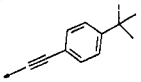
400	rac	
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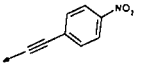
403	rac	
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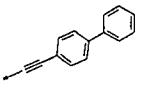
406	rac	
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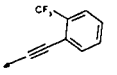
409	rac	
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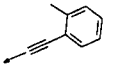
411	-	
412	rac	
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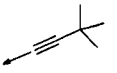
415	rac	
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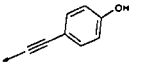
418	rac	
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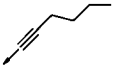
420	-	

N°	Racémico o enantiómero	R3
421	rac	
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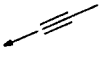
424	rac	
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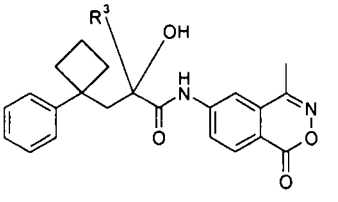

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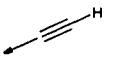
427	rac	
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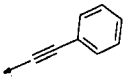
430	rac	
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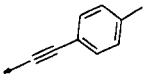
433	rac	
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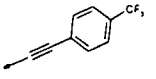
436	rac	
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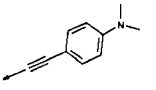
439	rac	
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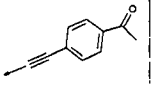
442	rac	
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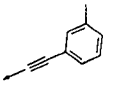
445	rac	
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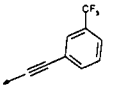
448	rac	
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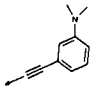
451	rac	
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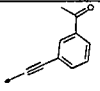
453	-	
454	rac	
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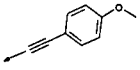
457	rac	
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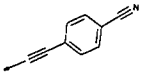
460	rac	
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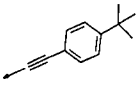
463	rac	
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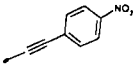
466	rac	
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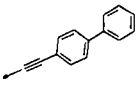
469	rac	
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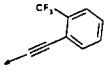
472	rac	
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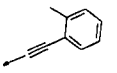
475	rac	
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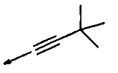
478	rac	
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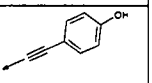
481	rac	
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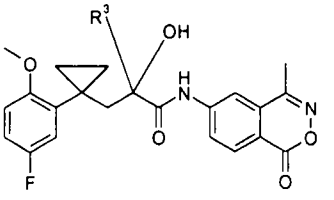
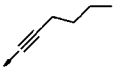
483	-	



N°	Racémico o enantiómero	R3
484	rac	
485	-	
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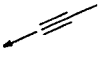
487	rac	
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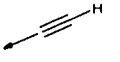
490	rac	
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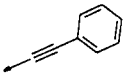
493	rac	
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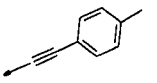
496	rac	
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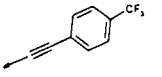
499	rac	
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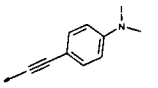
502	rac	
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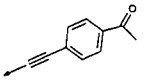
505	rac	
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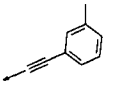
508	rac	
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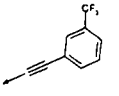
511	rac	
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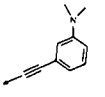
514	rac	
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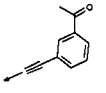
517	rac	
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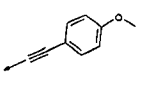
520	rac	

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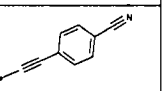
523	rac	
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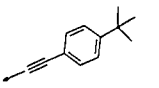
526	rac	
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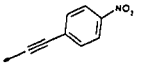
529	rac	
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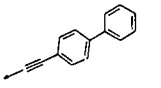
532	Rac	
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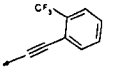
535	rac	
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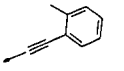
538	rac	
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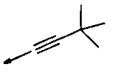
541	rac	
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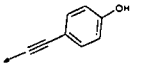
544	rac	

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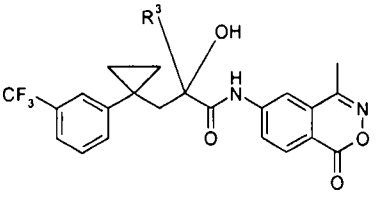
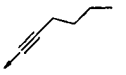


N°	Racémico o enantiómero	R3
547	rac	
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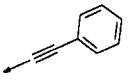
556	Rac	
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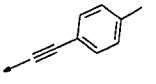
559	Rac	
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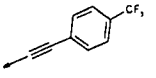
562	Rac	
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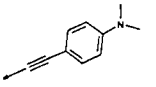
565	Rac	
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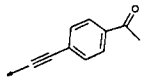
568	Rac	
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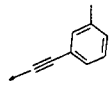
571	Rac	
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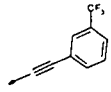
574	Rac	
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576	-	
577	Rac	
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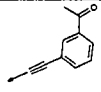
579	-	
580	Rac	
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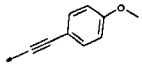
583	Rac	
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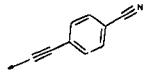
586	Rac	
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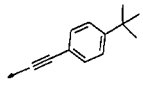
589	Rac	
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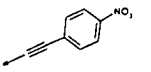
592	Rac	
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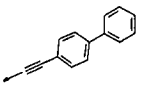
595	Rac	
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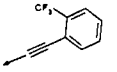
598	rac	
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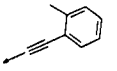
601	rac	
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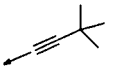
604	rac	
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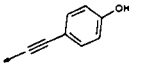
607	rac	
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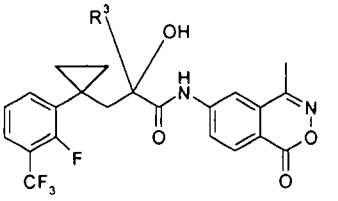
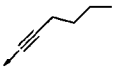


N°	Racémico o enantiómero	R3
610	rac	
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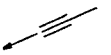
613	rac	
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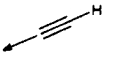
616	rac	
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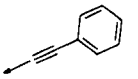
619	rac	
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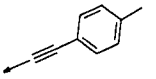
622	rac	
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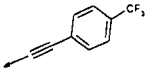
625	rac	
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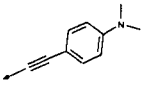
628	rac	
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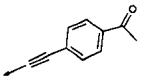
631	rac	
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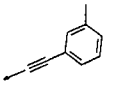
634	rac	
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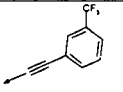
636	-	
637	rac	

370

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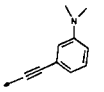
640	rac	
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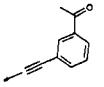
643	rac	
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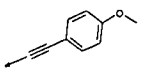
646	rac	
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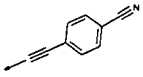
649	rac	
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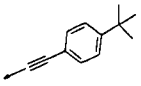
652	rac	
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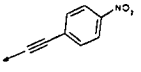
655	rac	
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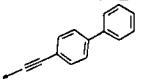
658	rac	
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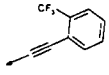
661	rac	

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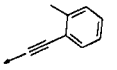
664	rac	
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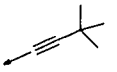
667	rac	
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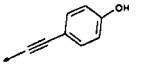
670	rac	
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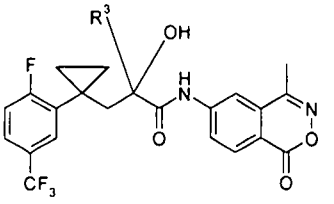
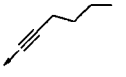
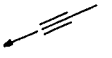


N°	Racémico o enantiómero	R3
673	rac	
674	-	
675	+	
676	rac	
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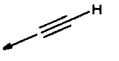
679	rac	
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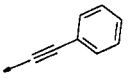
682	rac	
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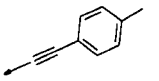
685	rac	
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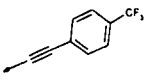
688	rac	
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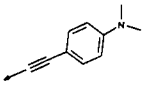
691	rac	
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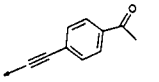
694	rac	
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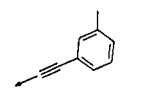
697	rac	
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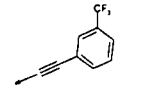
700	rac	
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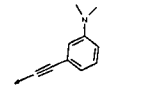
703	rac	
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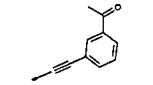
706	rac	
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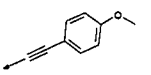
709	rac	
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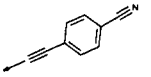
712	rac	
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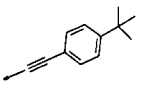
715	rac	
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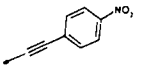
718	rac	
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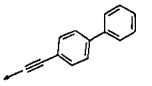
721	rac	
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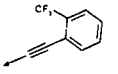
724	rac	
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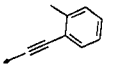
727	rac	
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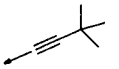
730	rac	
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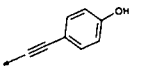
733	rac	
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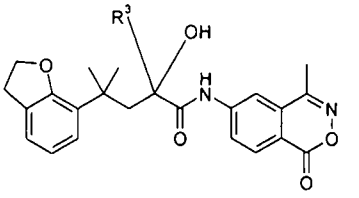
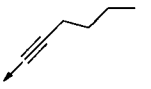


N°	Racémico o enantiómero	R3
736	rac	
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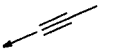
738	+	
739	rac	
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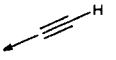
742	rac	
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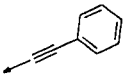
745	rac	
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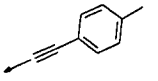
748	rac	
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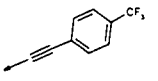
751	rac	
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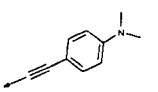
753	-	
754	rac	

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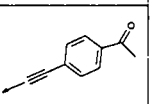
756	-	
757	rac	
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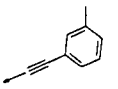
759	-	
760	rac	
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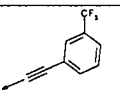
763	rac	
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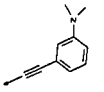
766	rac	
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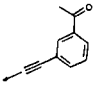
768	-	
769	rac	
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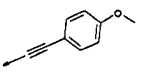
772	rac	
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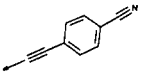
775	rac	
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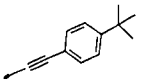
778	rac	
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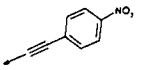
781	rac	
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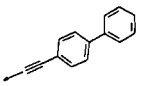
784	rac	
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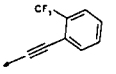
787	rac	
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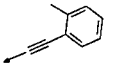
790	rac	
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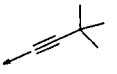
793	rac	
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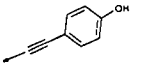
796	rac	
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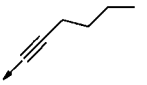
N°	Racémico o enantiómero	R3
799	rac	
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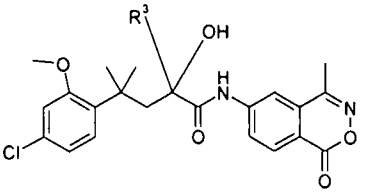

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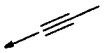
802	rac	
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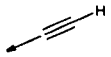
805	rac	
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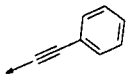
808	rac	
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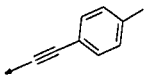
811	rac	
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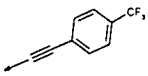
814	rac	
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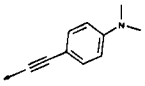
817	rac	
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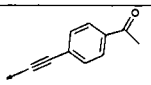
820	rac	
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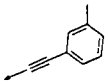
823	rac	
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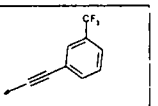
826	rac	
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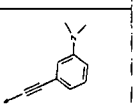
829	rac	
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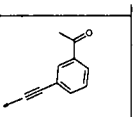
832	rac	
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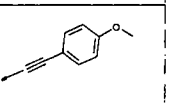
835	rac	
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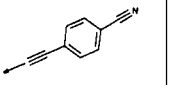
838	rac	
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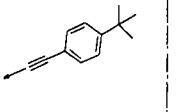
841	rac	
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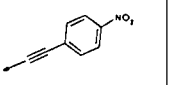
844	rac	
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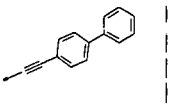
847	rac	
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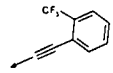
850	rac	
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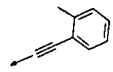
853	rac	
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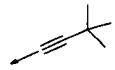
856	rac	
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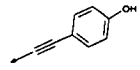
859	rac	
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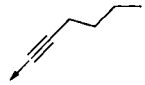
861	-	

N°	Racémico o enantiómero	R3
862	rac	
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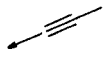
865	rac	
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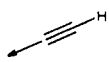
868	rac	
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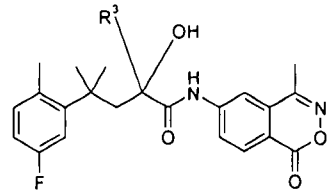
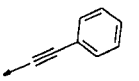


871	rac	
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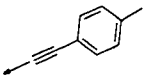
874	rac	
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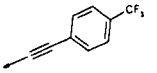
877	rac	
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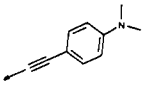
880	rac	
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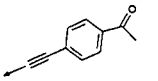
883	rac	
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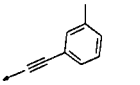
886	rac	
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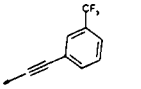
889	rac	
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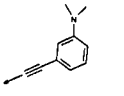
892	rac	
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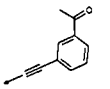
895	rac	
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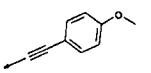
898	rac	
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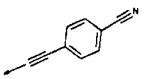
901	rac	
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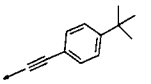
904	rac	
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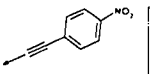
907	rac	
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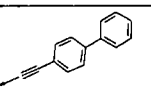
910	rac	
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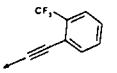
913	rac	
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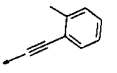
916	rac	
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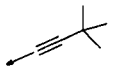
918	-	

919	rac	
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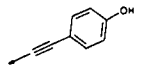
922	rac	
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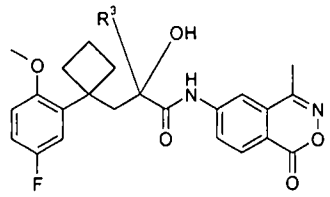
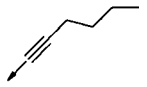
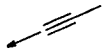


N°	Racémico o enantiómero	R3
925	rac	
926	-	
927	+	
928	rac	
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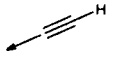
931	rac	
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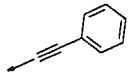
933	-	
934	rac	
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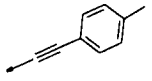
936	-	
937	rac	
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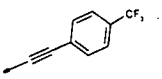
939	-	

940	rac	
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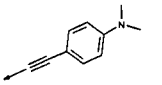
943	rac	
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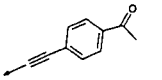
945	-	
946	rac	
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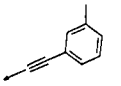
949	rac	
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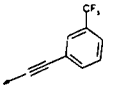
952	rac	
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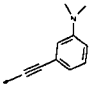
954	-	
955	rac	
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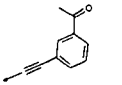
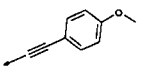
957	-	
958	rac	
959	+	
960	-	
961	rac	
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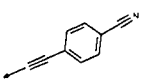
964	rac	

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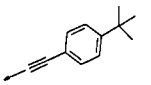
967	rac	
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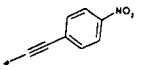
969	-	
970	rac	
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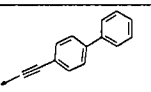
972	-	
973	rac	
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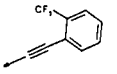
975	-	
976	rac	
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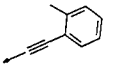
978	-	
979	rac	
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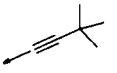
981	-	
982	rac	
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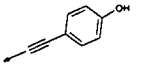
985	rac	
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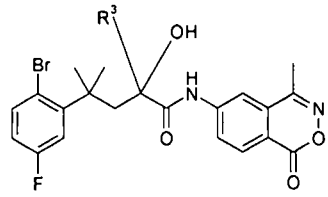
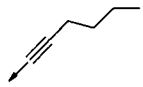
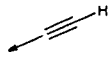
987	-	



N°	Racémico o enantiómero	R3
988	rac	
989	-	
990	+	
991	rac	
992	+	
993	-	
994	rac	
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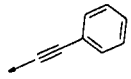
997	rac	
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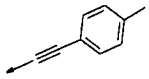
999	-	
1000	rac	
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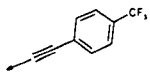
1002	-	
1003	rac	
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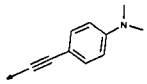
1006	rac	
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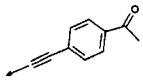
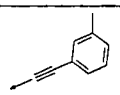
1008	-	
1009	rac	
1010	+	

1011	-	
1012	rac	
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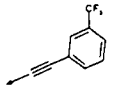
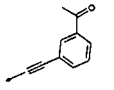
1014	-	
1015	rac	
1016	+	
1017	-	
1018	rac	
1019	+	
1020	-	
1021	rac	
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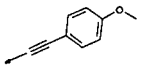
1023	-	
1024	rac	
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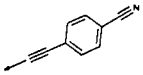
1027	rac	
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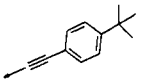
1029	-	
1030	rac	
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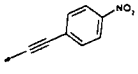
1033	rac	
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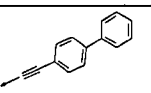
1035	-	

1036	rac	
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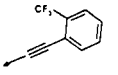
1038	-	
1039	rac	
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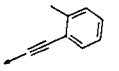
1042	rac	
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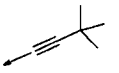
1045	rac	
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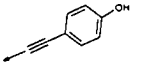
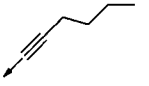
1048	rac	
1049	+	
1050	-	

N°	Racémico o enantiómero	R3
1051	rac	
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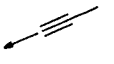
1054	rac	
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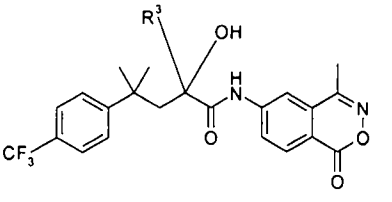
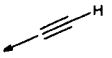


1057	rac	
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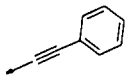
1060	rac	
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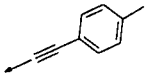
1063	rac	
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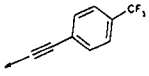
1066	rac	
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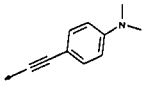
1069	rac	
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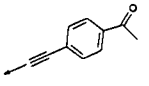
1072	rac	
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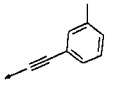
1075	rac	
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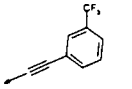
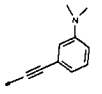
1078	rac	
1079	+	
1080	-	

1081	rac	
1082	+	
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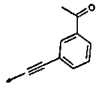
1084	rac	
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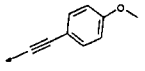
1087	rac	
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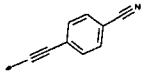
1089	-	
1090	rac	
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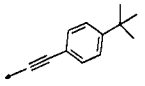
1093	rac	
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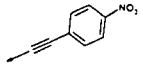
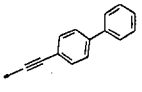
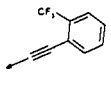
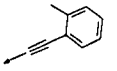
1096	rac	
1097	+	
1098	-	
1099	rac	
1100	+	
1101	-	
1102	rac	
1103	+	
1104	-	

390

1105	rac	
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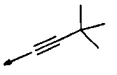
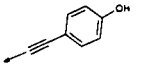
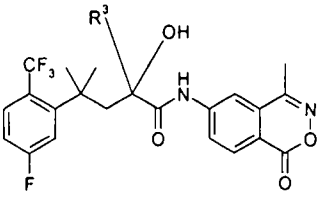
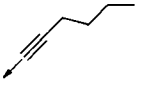
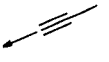
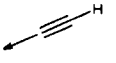
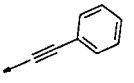
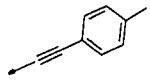
1107	-	
1108	rac	
1109	+	
1110	-	
1111	rac	
1112	+	
1113	-	



N°	Racémico o enantiómero	R3
1114	rac	
1115	-	
1116	+	
1117	rac	
1118	+	
1119	-	
1120	rac	
1121	+	
1122	-	
1123	rac	
1124	+	
1125	-	

1126	rac	
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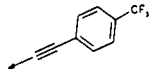
1128	-	
1129	rac	
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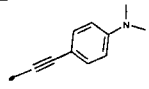
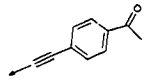
1132	rac	
1133	+	
1134	-	
1135	rac	
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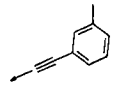
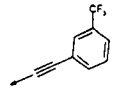
1137	-	
1138	rac	
1139	+	
1140	-	
1141	rac	
1142	+	
1143	-	
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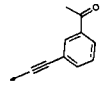
1145	+	
1146	-	
1147	rac	
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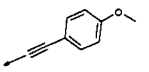
1149	-	

1150	rac	
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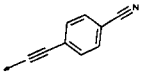
1153	rac	
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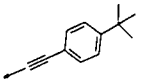
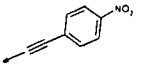
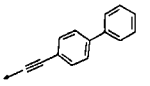
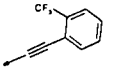
1156	rac	
1157	+	
1158	-	
1159	rac	
1160	+	
1161	-	
1162	rac	
1163	+	
1164	-	
1165	rac	
1166	+	
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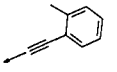
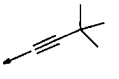
1168	rac	
1169	+	
1170	-	
1171	rac	
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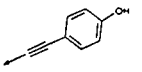
1174	rac	
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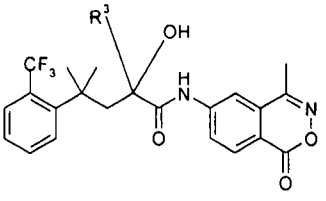
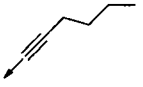
1176	-	



N°	Racémico o enantiómero	R3
1177	rac	
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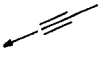
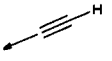
1179	+	
1180	rac	
1181	+	
1182	-	
1183	rac	
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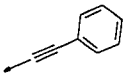
1185	-	
1186	rac	
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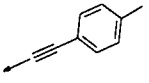
1188	-	
1189	rac	
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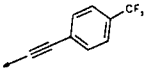
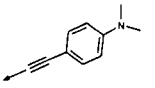
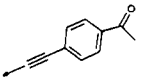
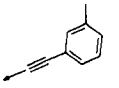
1191	-	
1192	rac	
1193	+	
1194	-	

1195	rac	
1196	+	
1197	-	
1198	rac	
1199	+	
1200	-	
1202	rac	
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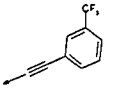
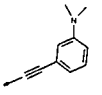
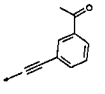
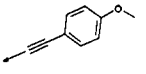
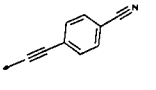
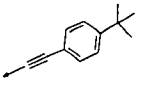
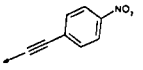
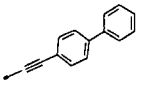
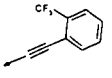
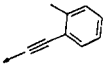
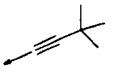
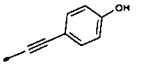
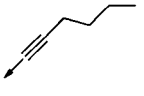
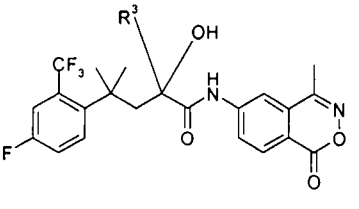
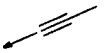
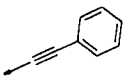
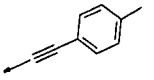
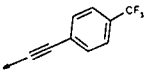
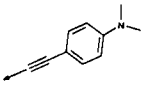
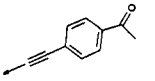
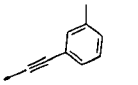
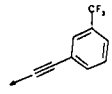
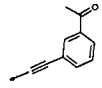
1204	rac	
1205	+	
1206	-	
1207	rac	
1208	+	
1209	-	
1210	rac	
1211	+	
1212	-	
1213	rac	
1214	+	
1215	-	
1216	rac	
1217	+	
1218	-	
1219	rac	

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	-	

N°	Racémico o enantiómero	R3
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	-	
1261	rac	
1262	+	
1263	-	
1264	rac	
1265	+	

1266	-	
1267	rac	
1268	+	
1269	-	
1270	rac	
1271	+	
1272	-	
1273	rac	
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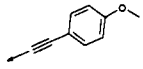
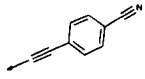
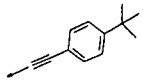
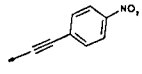
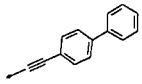
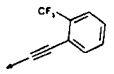
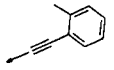
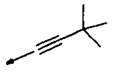
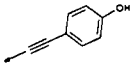
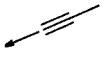
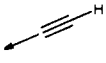
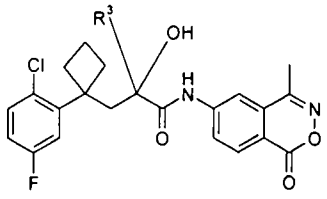
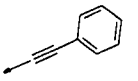
1275	-	
1276	rac	
1277	+	
1278	-	
1279	rac	
1280	+	
1281	-	
1282	rac	
1283	+	
1284	-	
1285	rac	
1286	+	
1287	-	
1288	rac	
1289	+	
1290	-	

1291	rac	
1292	+	
1293	-	
1294	rac	
1295	+	
1296	-	
1297	rac	
1298	+	
1299	-	
1300	rac	
1301	+	
1302	-	

N°	Racémico o enantiómero	R3
1303	rac	
1304	-	
1305	+	
1306	rac	
1307	+	
1308	-	
1309	rac	
1310	+	
1311	-	



1312	rac	
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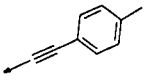
1314	-	
1315	rac	
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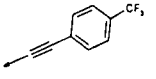
1318	rac	
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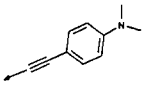
1321	rac	
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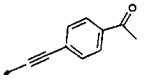
1324	rac	
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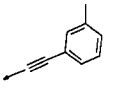
1327	rac	
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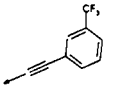
1330	rac	
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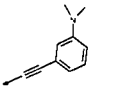
1333	rac	
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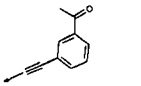
1336	rac	

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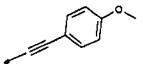
1339	rac	
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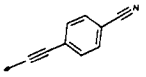
1342	rac	
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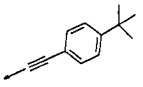
1345	rac	
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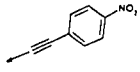
1348	rac	
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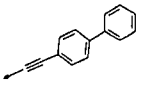
1351	rac	
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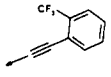
1354	rac	
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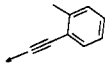
1357	rac	
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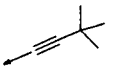
1361	+	
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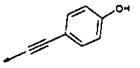
1362	rac	
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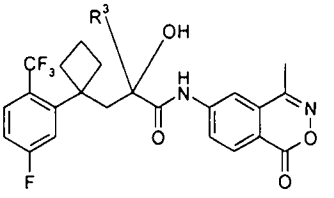
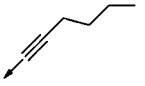


N°	Racémico o enantiómero	R3
1366	rac	
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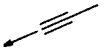
1369	rac	
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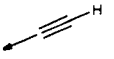
1372	rac	
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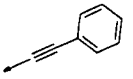
1375	rac	
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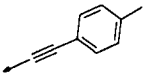
1378	rac	
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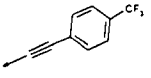
1381	rac	
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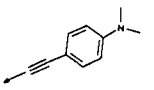
1384	rac	
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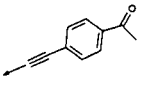
1387	rac	
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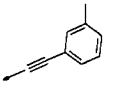
1390	rac	
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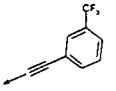
1393	rac	
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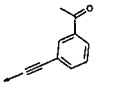
1399	rac	
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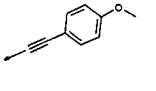
1402	rac	
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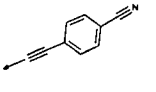
1405	rac	
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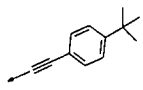
1408	rac	
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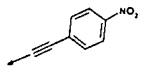
1411	rac	
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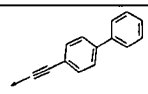
1414	rac	
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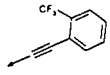
1417	rac	
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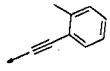
1420	rac	
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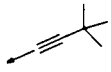
1423	rac	
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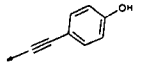
1426	rac	
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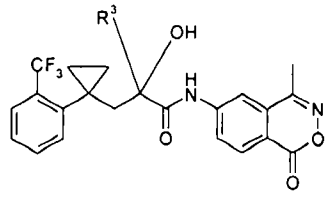
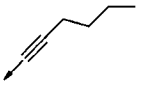
1428	-	

N°	Racémico o enantiómero	R3



1429	rac	
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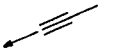
1432	rac	
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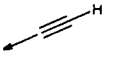
1435	rac	
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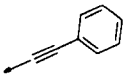
1438	rac	
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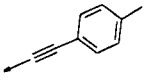
1441	rac	
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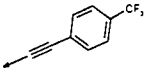
1444	rac	
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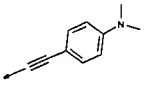
1447	rac	
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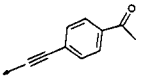
1450	rac	
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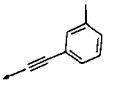
1453	rac	

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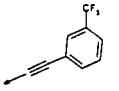
1456	rac	
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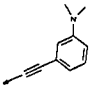
1459	rac	
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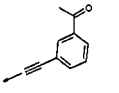
1462	rac	
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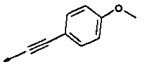
1465	rac	
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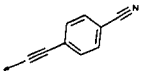
1468	rac	
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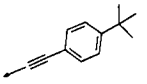
1471	rac	
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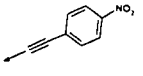
1474	rac	
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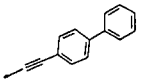
1477	rac	
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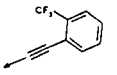
1479	-	
1480	rac	
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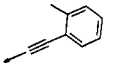
1483	rac	
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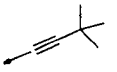
1485	-	
1486	rac	
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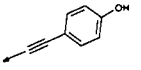
1488	-	
1489	rac	
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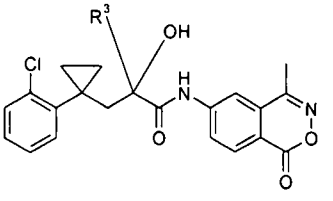
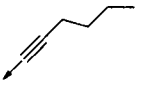
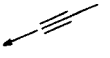


N°	Racémico o enantiómero	R3
1492	rac	
1493	-	
1494	+	
1495	rac	
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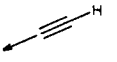
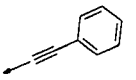
1497	-	
1498	rac	
1499	+	

1500	-	
1501	rac	
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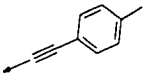
1503	-	
1504	rac	
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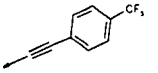
1507	rac	
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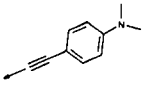
1510	rac	
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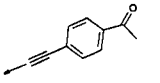
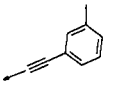
1513	rac	
1514	+	
1515	-	
1516	rac	
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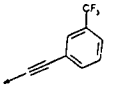
1519	rac	
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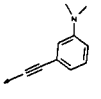
1522	rac	
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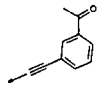
1525	rac	
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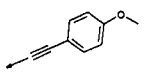
1528	rac	
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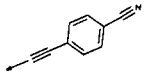
1530	-	
1531	rac	
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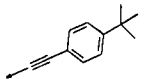
1533	-	
1534	rac	
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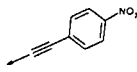
1537	rac	
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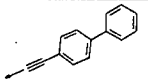
1539	-	
1540	rac	
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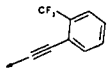
1542	-	
1543	rac	
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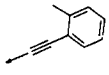
1546	rac	
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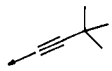
1549	rac	
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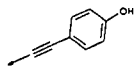
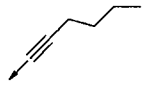
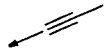
1552	rac	
1553	+	
1554	-	

N°	Racémico o enantiómero	R3
1555	rac	
1556	-	
1557	+	
1558	rac	
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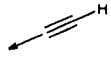
1560	-	
1561	rac	
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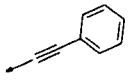
1564	rac	
1565	+	
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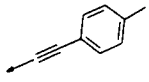
1567	rac	
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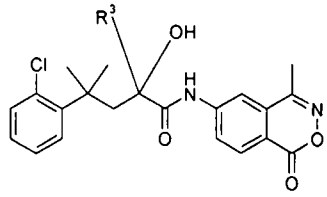
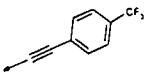
1569	-	



1570	rac	
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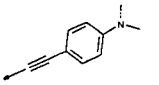
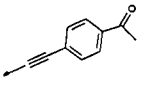
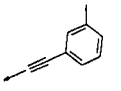
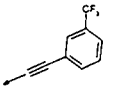
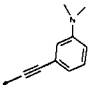
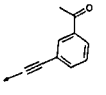
1572	-	
1573	rac	
1574	+	
1575	-	
1576	rac	
1577	+	
1578	-	
1579	rac	
1580	+	
1581	-	
1582	rac	
1583	+	
1584	-	
1585	rac	
1586	+	
1587	-	
1588	rac	
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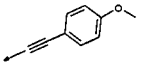
1590	-	
1591	rac	
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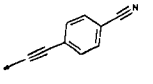
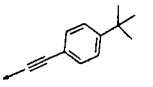
1593	-	
1594	rac	

1595	+	
1596	-	
1597	rac	
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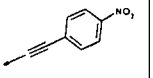
1599	-	
1600	rac	
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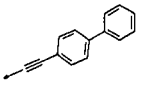
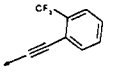
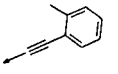
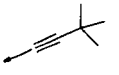
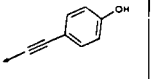
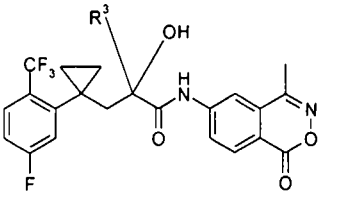
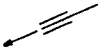
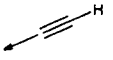
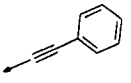
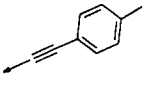
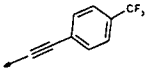
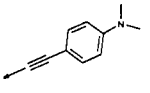
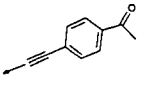
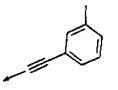
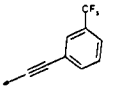
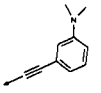
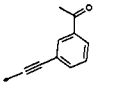
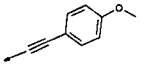
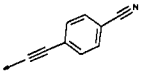
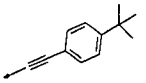
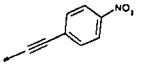
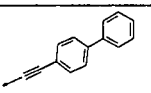
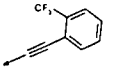
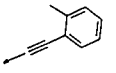
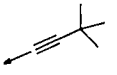
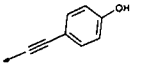
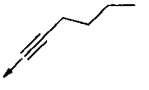
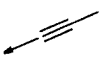
1602	-	
1603	rac	
1604	+	
1605	-	
1606	rac	
1607	+	
1608	-	
1609	rac	
1610	+	
1611	-	
1612	rac	
1613	+	
1614	-	
1615	rac	
1616	+	
1617	-	

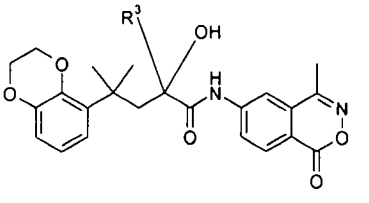


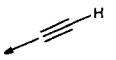
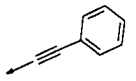
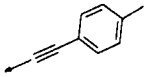
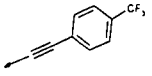
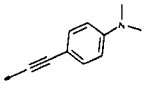
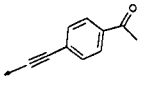
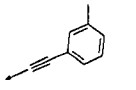
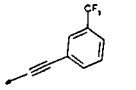
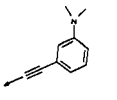
N°	Racémico o enantiómero	R3
1618	rac	
1619	-	
1620	+	
1621	rac	
1622	+	
1623	-	
1624	rac	
1625	+	
1626	-	
1627	rac	
1628	+	
1629	-	
1630	rac	
1631	+	
1632	-	
1633	rac	
1634	+	
1635	-	
1636	rac	
1637	+	
1638	-	
1639	rac	
1640	+	

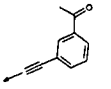
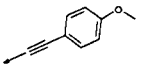
1641	-	
1642	rac	
1643	+	
1644	-	
1645	rac	
1646	+	
1647	-	
1648	rac	
1649	+	
1650	-	
1651	rac	
1652	+	
1653	-	
1654	rac	
1655	+	
1656	-	
1657	rac	
1658	+	
1659	-	
1660	rac	
1661	+	
1662	-	
1663	rac	
1664	+	
1665	-	

1666	rac	
1667	+	
1668	-	
1669	rac	
1670	+	
1671	-	
1672	rac	
1673	+	
1674	-	
1675	rac	
1676	+	
1677	-	
1678	rac	
1679	+	
1680	-	

N°	Racémico o enantiómero	R3
1681	rac	
1682	-	
1683	+	
1684	rac	
1685	+	
1686	-	



1687	rac	
1688	+	
1689	-	
1690	rac	
1691	+	
1692	-	
1693	rac	
1694	+	
1695	-	
1696	rac	
1697	+	
1698	-	
1699	rac	
1700	+	
1701	-	
1702	rac	
1703	+	
1704	-	
1705	rac	
1706	+	
1707	-	
1708	rac	
1709	+	
1710	-	
1711	rac	

1712	+	
1713	-	
1714	rac	
1715	+	
1716	-	
1717	rac	
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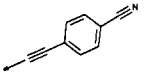
1720	rac	
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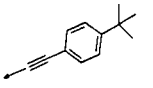
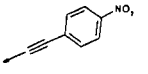
1722	-	
1723	rac	
1724	+	
1725	-	
1726	rac	
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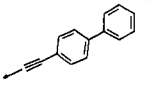
1729	rac	
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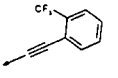
1731	-	
1732	rac	
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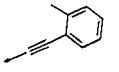
1735	rac	

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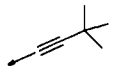
1738	rac	
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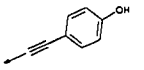
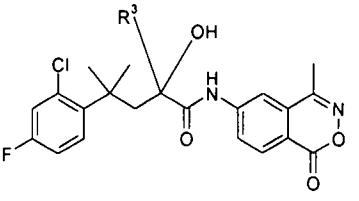
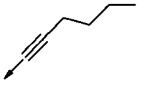
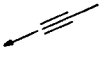
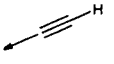
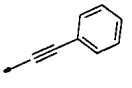
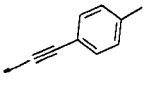
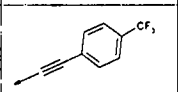
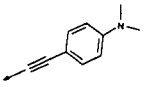
1741	rac	
1742	+	
1743	-	



N°	Racémico o enantiómero	R3
1744	rac	
1745	-	
1746	+	
1747	rac	
1748	+	
1749	-	
1750	rac	
1751	+	
1752	-	
1753	rac	
1754	+	
1755	-	
1756	rac	
1757	+	

1758	-	
1759	rac	
1760	+	
1761	-	
1762	rac	
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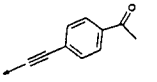
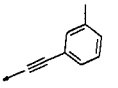
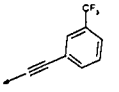
1764	-	
1765	rac	
1766	+	
1767	-	
1768	rac	
1769	+	
1770	-	
1771	rac	
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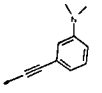
1773	-	
1774	rac	
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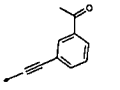
1777	rac	
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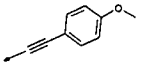
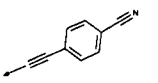
1780	rac	
1781	+	
1782	-	

1783	rac	
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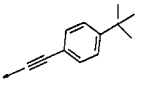
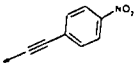
1785	-	
1786	rac	
1787	+	
1788	-	
1789	rac	
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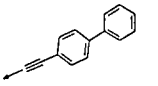
1792	rac	
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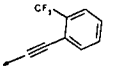
1794	-	
1795	rac	
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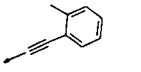
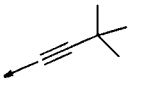
1797	-	
1798	rac	
1799	+	
1800	-	
1801	rac	
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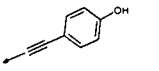
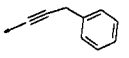
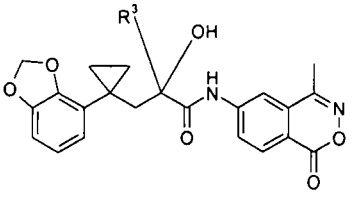
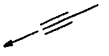
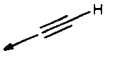
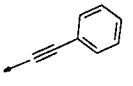
1803	-	
1804	rac	
1805	+	
1806	-	

A20

1807	rac	
1808	+	
1809	-	
1810	rac	
1811	+	
1812	-	



N°	Racémico o enantiómero	R3
1813	rac	
1814	-	
1815	+	
1816	rac	
1817	+	
1818	-	
1819	rac	
1820	+	
1821	-	
1822	rac	
1823	+	
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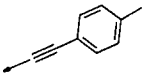
1825	rac	
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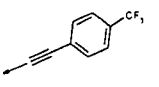
1828	rac	

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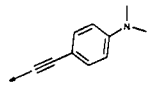
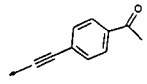
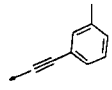
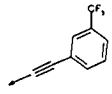
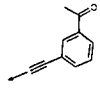
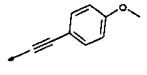
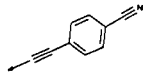
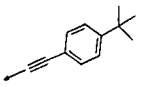
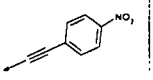
1830	-	
1831	rac	
1832	+	
1833	-	
1834	rac	
1835	+	
1836	-	
1837	rac	
1838	+	
1839	-	
1840	rac	
1841	+	
1842	-	
1843	rac	
1844	+	
1845	-	
1846	rac	
1847	+	
1848	-	
1849	rac	
1850	+	
1851	-	
1852	rac	
1853	+	

1854	-	
1855	rac	
1856	+	
1857	-	
1858	rac	
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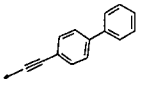
1860	-	
1861	rac	
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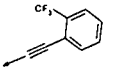
1863	-	
1864	rac	
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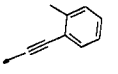
1866	-	
1867	rac	
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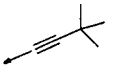
1869	-	
1870	rac	
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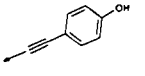
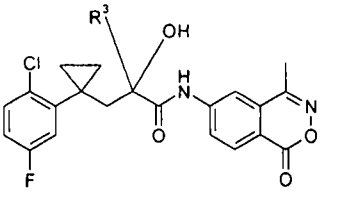
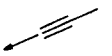
1872	-	
1873	rac	
1874	+	
1875	-	

N°	Racémico o	R3



	enantiómero	
1876	rac	
1877	-	
1878	+	
1879	rac	
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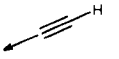
1882	rac	
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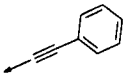
1885	rac	
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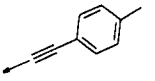
1888	rac	
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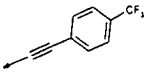
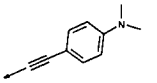
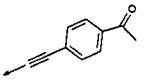
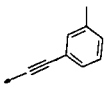
1891	rac	
1892	+	
1893	-	
1894	rac	
1895	+	
1896	-	
1897	rac	
1898	+	
1899	-	

1900	rac	
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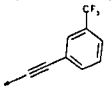
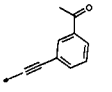
1902	-	
1903	rac	
1904	+	
1905	-	
1906	rac	
1907	+	
1908	-	
1909	rac	
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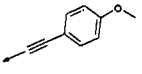
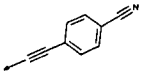
1911	-	
1912	rac	
1913	+	
1914	-	
1915	rac	
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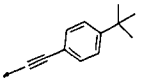
1917	-	
1918	rac	
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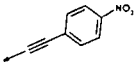
1920	-	
1921	rac	
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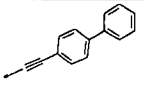
1923	-	
1924	rac	

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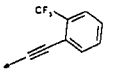
1926	-	
1927	rac	
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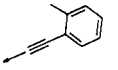
1929	-	
1930	rac	
1931	+	
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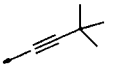
1933	rac	
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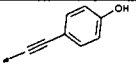
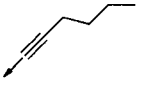
1935	-	
1936	rac	
1937	+	
1938	-	

N°	Racémico o enantiómero	R3
1939	rac	
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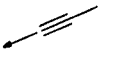
1941	+	
1942	rac	
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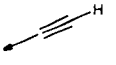
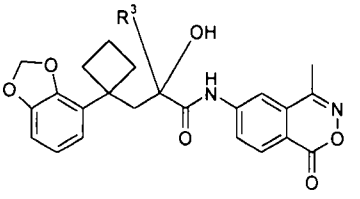
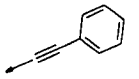
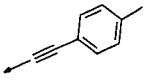
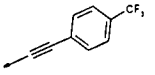
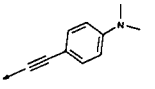
1944	-	
1945	rac	



1946	+	
1947	-	
1948	rac	
1949	+	
1950	-	
1951	rac	
1952	+	
1953	-	
1954	rac	
1955	+	
1956	-	
1957	rac	
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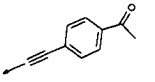
1959	-	
1960	rac	
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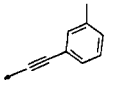
1963	rac	
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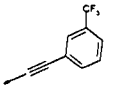
1966	rac	
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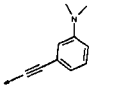
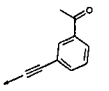
1968	-	
1969	rac	
1970	+	

1971	-	
1972	rac	
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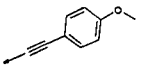
1974	-	
1975	rac	
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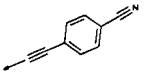
1977	-	
1978	rac	
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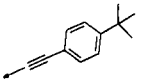
1981	rac	
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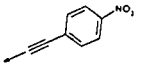
1983	-	
1984	rac	
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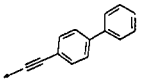
1986	-	
1987	rac	
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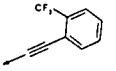
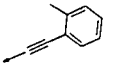
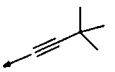
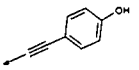
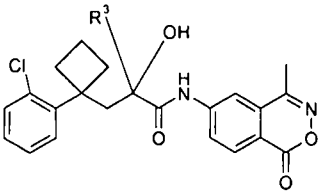
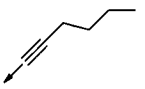
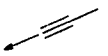
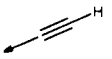
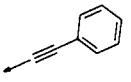
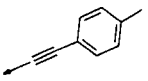
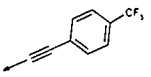
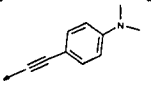
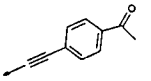
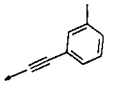
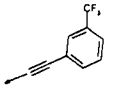
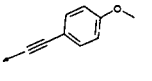
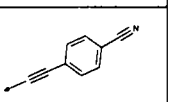
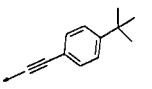
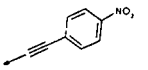
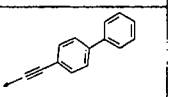
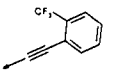
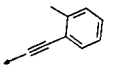
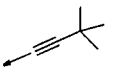
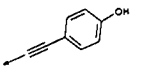
1989	-	
1990	rac	
1991	+	
1992	-	
1993	rac	
1994	+	

1995	-	
1996	rac	
1997	+	
1998	-	
1999	rac	
2000	+	
2001	-	

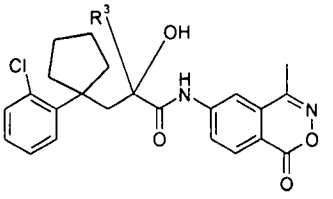


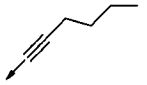
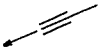
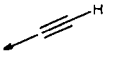
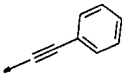
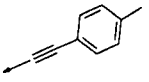
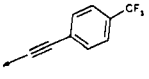
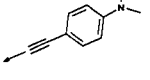
N°	Racémico o enantiómero	R3
2002	rac	
2003	-	
2004	+	
2005	rac	
2006	+	
2007	-	
2008	rac	
2009	+	
2010	-	
2011	rac	
2012	+	
2013	-	
2014	rac	
2015	+	

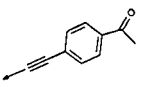
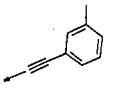
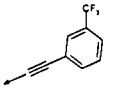
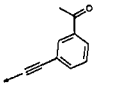
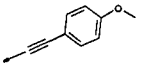
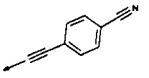
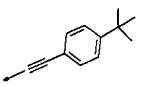
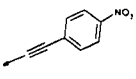
2016	-	
2017	rac	
2018	+	
2019	-	
2020	rac	
2021	+	
2022	-	
2023	rac	
2024	+	
2025	-	
2026	rac	
2027	+	
2028	-	
2029	rac	
2030	+	
2031	-	
2032	rac	
2033	+	
2034	-	
2035	rac	
2036	+	
2037	-	
2038	rac	
2039	+	

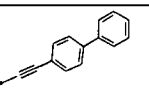
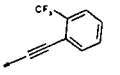
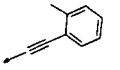
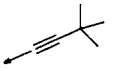
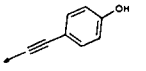
2040	-	
2041	rac	
2042	+	
2043	-	
2044	rac	
2045	+	
2046	-	
2047	rac	
2048	+	
2049	-	
2050	rac	
2051	+	
2052	-	
2053	rac	
2054	+	
2055	-	
2056	rac	
2057	+	
2058	-	
2059	rac	
2060	+	
2061	-	
2062	rac	
2063	+	

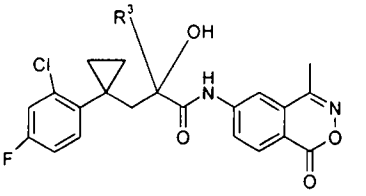
2064	-	

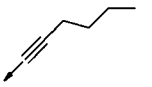
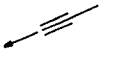


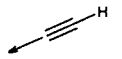
N°	Racémico o enantiómero	R3
2065	rac	
2066	-	
2067	+	
2068	rac	
2069	+	
2070	-	
2071	rac	
2072	+	
2073	-	
2074	rac	
2075	+	
2076	-	
2077	rac	
2078	+	
2079	-	
2080	rac	
2081	+	
2082	-	
2083	rac	
2084	+	
2085	-	

2086	rac	
2087	+	
2088	-	
2089	rac	
2090	+	
2091	-	
2092	rac	
2093	+	
2094	-	
2095	rac	
2096	+	
2097	-	
2098	rac	
2099	+	
2100	-	
2101	rac	
2102	+	
2103	-	
2104	rac	
2105	+	
2106	-	
2107	rac	
2108	+	
2109	-	
2110	rac	

2111	+	
2112	-	
2113	rac	
2114	+	
2115	-	
2116	rac	
2117	+	
2118	-	
2119	rac	
2120	+	
2121	-	
2122	rac	
2123	+	
2124	-	
2125	rac	
2126	+	
2127	-	



N°	Racémico o enantiómero	R3
2128	rac	
2129	-	
2130	+	
2131	rac	

2132	+	
2133	-	
2134	rac	
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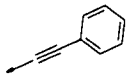
2137	rac	
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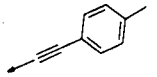
2140	rac	
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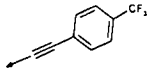
2142	-	
2143	rac	
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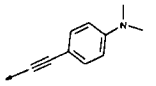
2145	-	
2146	rac	
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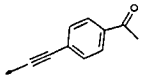
2149	rac	
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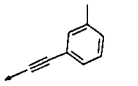
2152	rac	
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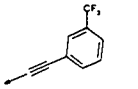
2155	rac	
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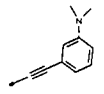
2157	-	
2158	rac	
2159	+	
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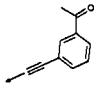
2161	rac	
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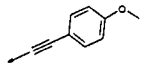
2164	rac	
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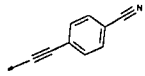
2167	rac	
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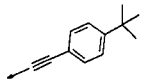
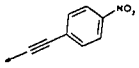
2170	rac	
2171	+	
2172	-	
2173	rac	
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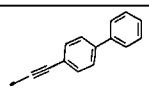
2176	rac	
2177	+	
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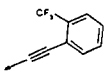
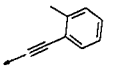
2179	rac	
2180	+	

2181	-	
2182	rac	
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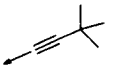
2185	rac	
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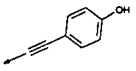
2188	rac	
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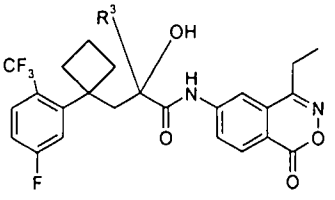
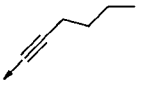
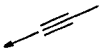
2190	-	



N°	Racémico o enantiómero	R3
2191	rac	
2192	-	
2193	+	
2194	rac	
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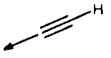
2196	-	
2197	rac	
2198	+	
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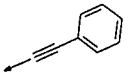
2200	rac	
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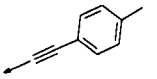
2202	-	
2203	rac	
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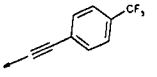
2205	-	
2206	rac	
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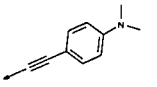
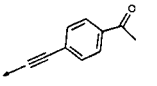
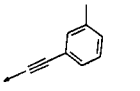
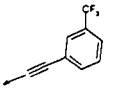
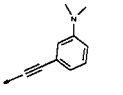
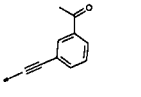
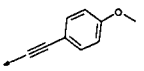
2208	-	
2209	rac	
2210	+	
2211	-	
2212	rac	
2213	+	
2214	-	
2215	rac	
2216	+	
2217	-	
2218	rac	
2219	+	
2220	-	
2221	rac	
2222	+	
2223	-	
2224	rac	
2225	+	
2226	-	

2227	rac	
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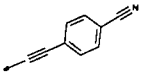
2229	-	
2230	rac	
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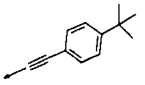
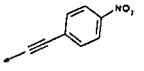
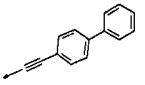
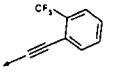
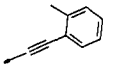
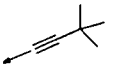
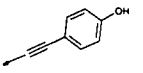
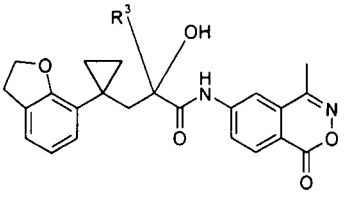
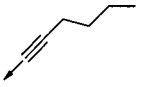
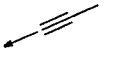
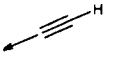
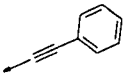
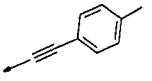
2232	-	
2233	rac	
2234	+	
2235	-	
2236	rac	
2237	+	
2238	-	
2239	rac	
2240	+	
2241	-	
2242	rac	
2243	+	
2244	-	
2245	rac	
2246	+	
2247	-	
2248	rac	
2249	+	
2250	-	

2251	rac	
2252	+	
2253	-	



N°	Racémico o enantiómero	R3
2254	rac	
2255	-	
2256	+	
2257	rac	
2258	+	
2259	-	
2260	rac	
2261	+	
2262	-	
2263	rac	
2264	+	
2265	-	
2266	rac	
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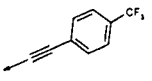
2269	rac	
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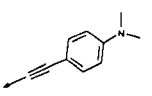
2272	rac	

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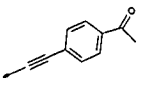
2273	rac	
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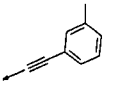
2278	rac	
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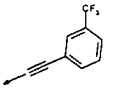
2281	rac	
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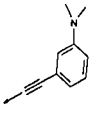
2284	rac	
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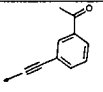
2287	rac	
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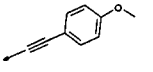
2290	rac	
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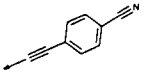
2293	rac	
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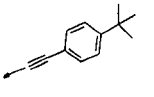
2296	rac	
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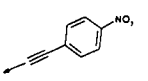
2298	-	
2299	rac	
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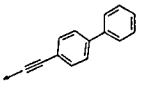
2301	-	
2302	rac	
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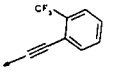
2304	-	
2305	rac	
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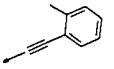
2307	-	
2308	rac	
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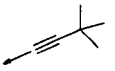
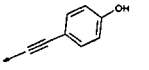
2310	-	
2311	rac	
2312	+	
2313	-	
2314	rac	
2315	+	
2316	-	

N°	Racémico o enantiómero	R3
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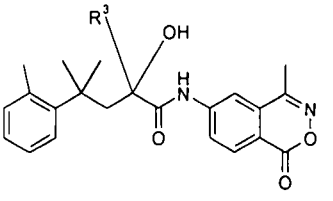
2318	-	



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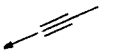
2320	rac	
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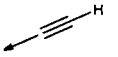
2323	rac	
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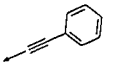
2325	-	
2326	rac	
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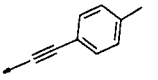
2329	rac	
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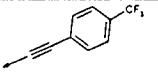
2332	rac	
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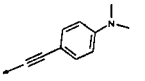
2334	-	
2335	rac	
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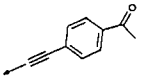
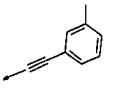
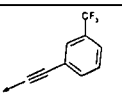
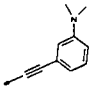
2338	rac	
2339	+	
2340	-	
2341	rac	
2342	+	
2343	-	

2344	rac	
2345	+	
2346	-	
2347	rac	
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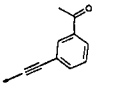
2349	-	
2350	rac	
2351	+	
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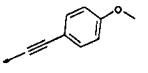
2353	rac	
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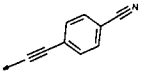
2355	-	
2356	rac	
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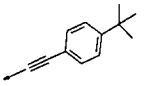
2358	-	
2359	rac	
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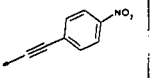
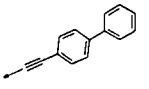
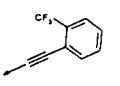
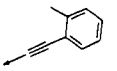
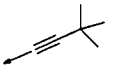
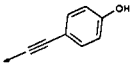
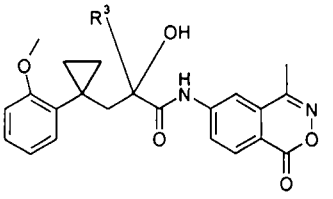
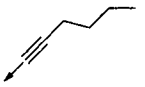
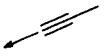
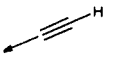
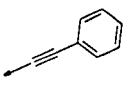
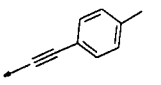
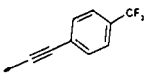
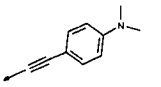
2361	-	
2362	rac	
2363	+	
2364	-	
2365	rac	
2366	+	
2367	-	
2368	rac	

2369	+	
2370	-	
2371	rac	
2372	+	
2373	-	
2374	rac	
2375	+	
2376	-	
2377	rac	
2378	+	
2379	-	



N°	Racémico o enantiómero	R3
2380	rac	
2381	-	
2382	+	
2383	rac	
2384	+	
2385	-	
2386	rac	
2387	+	
2388	-	
2389	rac	

2390	+	
2391	-	
2392	rac	
2393	+	
2394	-	
2395	rac	
2396	+	
2397	-	
2398	rac	
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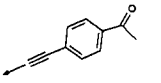
2401	rac	
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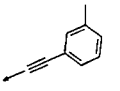
2404	rac	
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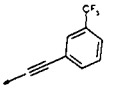
2407	rac	
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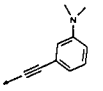
2410	rac	
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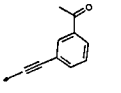
2413	rac	
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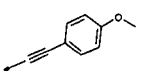
2416	rac	
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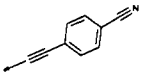
2419	rac	
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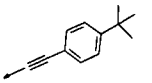
2422	rac	
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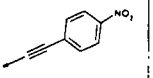
2425	rac	
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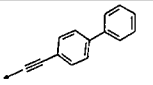
2428	rac	
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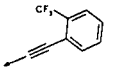
2431	rac	
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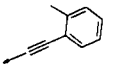
2434	rac	
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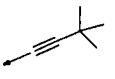
2437	rac	
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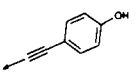
2439	-	
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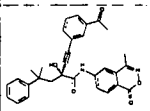
N°	Racémico o enantiómero	Estructura
2443	Rac	
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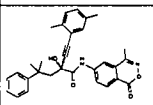
2446	Rac	
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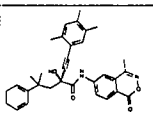
2449	Rac	
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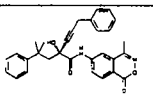
2452	Rac	
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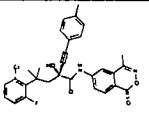
2455	Rac	
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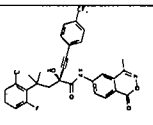
2458	Rac	
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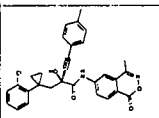
2461	Rac	
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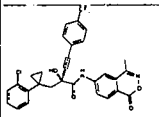
2464	Rac	
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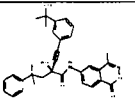
2467	Rac	
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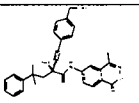
2470	Rac	
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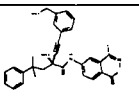
2473	Rac	
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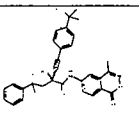
2476	Rac	
2477	+	
2478	-	

14. Composiciones farmacéuticas que contienen al menos un compuesto de la fórmula general I de acuerdo con una de las reivindicaciones 1 a 13 y opcionalmente al menos otra sustancia activa conjuntamente con coadyuvantes y/o vehículos farmacéuticos aceptables.

15. Una composición farmacéutica de acuerdo con la

reivindicación 14 en la cual el ingrediente activo adicional es un SERM (modulador selectivo del receptor de estrógeno), un inhibidor de aromatasa, un antiestrógeno o una prostaglandina.

16. Una 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 (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-pentafluorpentil)sulfanil]propil}amino)pentil] estra-1,3,5(10)-trien-3,17beta-diol (WO98/07740), 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 (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 (WO 03/045972), clomifen, raloxifen, así como otros compuestos con efecto antiestrógeno e inhibidores de la aromatasa tales como por ejemplo, fadrozol, formestano, letrozol, anastrozol o atamestano.

17. Uso de compuestos de una de las reivindicaciones 1 a 13 que es para preparar un medicamento.

18. Uso de compuestos de acuerdo con la reivindicación

17 que es para preparar un medicamento para la terapia y la prevención de enfermedades ginecológicas como endometriosis, leiomiomas del útero, sangrados disfuncionales y dismenorrea.

19. Uso de compuestos de acuerdo con la reivindicación 17 que es para preparar un medicamento para la terapia y la prevención de tumores hormona-dependientes.

20. Uso de compuestos de acuerdo con la reivindicación 17 que es para preparar un medicamento para la terapia y la prevención de carcinomas de mama.

21. Uso de compuestos de acuerdo con la reivindicación 17 que es para preparar un medicamento para la terapia y la prevención de carcinomas del endometrio.

22. Uso de compuestos de acuerdo con la reivindicación 17 que es para preparar un medicamento para la terapia y la prevención de carcinomas de ovario.

23. Uso de compuestos de acuerdo con la reivindicación 17 que es para preparar un medicamento para la terapia y la prevención de carcinomas de próstata.

24. Uso de compuestos de acuerdo con la reivindicación 17 que es para preparar un medicamento para la terapia de sustitución hormonal femenina.

25. Uso de compuestos de acuerdo con la reivindicación 17 que es para el control de la fertilidad femenina.

26. Proceso para la adición selectiva de litio alquinilo

TRATADO DE COOPERACIÓN INTERNACIONAL EN MATERIA DE PATENTES

De la OFICINA INTERNACIONAL

PCT

Notificación de registro de una modificación

(regla PCT 92bis.1 e
Instrucciones Administrativas , sección 422)

A:

BAYER SCHERING PHARMA
AKTIENGESELLSCHAFT
Patents and Licensing
13342 Berlin
ALEMANIA

Fecha de envío *(día/mes/año)*:

28 de agosto de 2007 (28/08/2007)

Referencia del solicitante o del agente:

53111AWO

NOTIFICACIÓN IMPORTANTE

Solicitud Internacional Nº:

PCT/EP 2006/006531

Fecha de presentación *(día/mes/año)*:

22 de junio de 2006 (22.06.2006)

1. Las siguientes indicaciones aparecen en los registros concernientes a:

☒ el solicitante ☐ el inventor ☐ el agente ☐ el representante común

Nombre y dirección:

SCHERING AKTIENGESELLSCHAFT
Müllestraße 178
13353 Berlín
Alemania

País de Nacionalidad: DE
País de Residencia: DE

Teléfono Nº:
030 46818718

Facsímil Nº:
030 46812058

Telex Nº:

2. La Oficina Internacional notifica por este medio al solicitante que se registró la siguiente modificación, concerniente a:

☐ la persona ☒ el nombre ☐ el domicilio ☐ la nacionalidad ☐ la residencia

Nombre y dirección:

BAYER SCHERING PHARMA AKTIENGESELLSCHAFT
Müllerstrasse 178
13353 Berlín
ALEMANIA

País de Nacionalidad: DE
País de Residencia: DE

Teléfono Nº:

Facsímil Nº:
030 46818718

Telex Nº:
030 46812058

3. Otras observaciones, si son necesarias:
El cambio mencionado también ha sido registrado con respecto a la dirección postal, tal como está indicada en el campo de domicilio ubicado al principio de este formulario.

4. Se envía una copia de esta notificación a:

☒ la Oficina receptora
☐ el Organismo de Búsqueda Internacional
☐ el Organismo de Examen Preliminar Internacional
☒ las Oficinas designadas concernientes
☐ las Oficinas seleccionadas concernientes
☐ otros:

La Oficina Internacional de WIPO
34, chemin des Colombettes
1211 Geneva 20, Suiza

Facsímil Nº: +41 22 338 82 70

Funcionario autorizado:

Nissen Diana
e-mail: *Diana.Nissen@wipo.int*
Teléfono Nº: *+41 22 338 96 66*

INFORME DE BÚSQUEDA INTERNACIONAL

Referencia Internacional

PCT/EP 2006/006531

A. CLASIFICACIÓN DEL OBJETO DE LA SOLICITUD

INV. C07D413/12 C07D265/02 A61K31/536 A61P5/34

Según la clasificación internacional de patentes (IPK) o la clasificación internacional la IPK

B. ÁMBITOS INVESTIGADOS

Material mínimo investigado (Sistema de clasificación y símbolos de clasificación)

A07D A61K A61P

Publicaciones investigadas pero no pertenecientes al material mínimo investigado, en tanto pertenezcan al ámbito investigado

Banco electrónico de datos consultado durante la búsqueda internacional (nombre del banco de datos y expresiones de búsqueda eventualmente empleadas)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. ANTECEDENTES CONSIDERADOS RELEVANTES

Categoría	Denominación de la publicación, así como, de ser requerido, indicación de los pasajes relevantes	Con referencia a reivindicación Nº
A	*EP 1 334 776 A (SCHERING AG [DE])* *17 de septiembre de 2003 (2003.09.17)* *resumen: párrafos [0001] - [0010];* *reivindicaciones; ejemplos*	*1-25*
A *X*	*WO 2005/003098 A1 (SCHERING AG [DE])* *13 de enero de 2005 (2005.01.13)* *resumen: página 1; reivindicaciones; ejemplos*	*1-25* *26*
X	*DATABASE BEILSTEIN* *Beilstein Institut zur Förderung der Wissenschaften, Francfort/Meno, DE* *XP002406053* *Acceso a Base de Datos Nº 1735553, 1964392, 2329868, 3529064 (RID);* *todo el documento* *& J. PHARM.SCI.* *vol. 82, Nº 6, 1993, páginas 605-609*	*26*

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☒ Otras publicaciones están listadas en la continuación del campo C

☒ Ver familia de patentes en el anexo

Categorías particulares indicadas en publicaciones

"A" publicación que define el estado general de la técnica pero no considerada como particularmente importante

"B" documento anterior pero publicado recién o después de la de la fecha de presentación internacional

"L" publicación adecuada para hacer aparecer como dudosa una reivindicación de prioridad, o mediante la cual debe ser considerada la fecha de divulgación de otra publicación mencionada en el informe de búsqueda o que es indicada por otra razón particular (como realizada)

"O" publicación que se refiere a una revelación oral, a una utilización, a una exposición o a otras disposiciones

"P" publicación realizada antes de la fecha de presentación internacional pero luego de la fecha de prioridad reivindicada

"T" publicaciones posteriores a las difundidas en la fecha de presentación internacional o de la fecha de prioridad y que no colisionan con la solicitud, sino que solo están indicadas para mayor entendimiento del principio fundamental de la invención o de la teoría sobre la cual se basa

"X" publicación de particular importancia: la invención reivindicada no puede ser considerada, solo como consecuencia de esta publicación, como novedosa o apoyarse en una actividad inventiva

"Y" publicación de particular importancia: la invención reivindicada no puede ser considerada como apoyada en una actividad inventiva cuando puede ser relacionada con una o varias otras publicaciones de esta categoría y tal relación es notoria para un especialista

"&" publicación que es miembro de la misma familia

Fecha de finalización de la búsqueda internacional	Fecha de envío del Informe de Búsqueda Internacional
7 de noviembre de 2006	*22/11/2006*
Nombre y Código Postal de ISA European Patent Office – P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel.: (+31-70) 340-2040; Tx: 31 651 epo nl Fax: (+31-70) 340-3016	**Funcionario Apoderado** *Weisbrod, Thomas*

INFORME DE BÚSQUEDA INTERNACIONAL

Referencia Internacional
PCT/EP 2006/006531

C. (continuación) **ANTECEDENTES CONSIDERADOS RELEVANTES**

Categoría	Denominación de la publicación, así como, de ser requerido, indicación de los pasajes relevantes	Con referencia a reivindicación Nº
X	*DATABASE BEILSTEIN* *Beilstein Institut zur Förderung der Wissenschaften, Francfort/Meno, DE* *XP002406062* *Acceso a Base de Datos Nº 2214047 (RID);* *todo el documento* *& J. CHEM. SOC. CHEM. COMMUN.,* *vol. 4, 1990, páginas 194-296*	*26*
X	*DATABASE BEILSTEIN* *Beilstein Institut zur Förderung der Wissenschaften, Francfort/Meno, DE* *XP002406063* *Acceso a Base de Datos Nº 4338477 (RID);* *todo el documento* *& J. HETEROCYCL. CHEM.,* *vol 32, Nº 4, 1995, páginas 1133-1140*	*26*
X	*DATABASE BEILSTEIN* *Beilstein Institut zur Förderung der Wissenschaften, Francfort/Meno, DE* *XP002406064* *Acceso a Base de Datos Nº 9573837 (RID);* *todo el documento* *& BIOORG. MED. CHEM.,* *vol. 11, Nº 18, 2003, páginas 4133-4142*	*26*
X	*DATABASE BEILSTEIN* *Beilstein Institut zur Förderung der Wissenschaften, Francfort/Meno, DE* *XP002406065* *Acceso a Base de Datos Nº 4064999 (RID);* *todo el documento* *& J. AM. CHEM. SOC.,* *vol. 32, Nº 4, 1995, páginas 10955-10965* *todo el docuemnto*	*26*

INFORME DE BÚSQUEDA INTERNACIONAL

Detalle de publicaciones que pertenecen a la misma familia de patentes

Referencia Internacional

PCT/EP 2006/006531

Documentos de Patente citados en el Informe de Búsqueda	Fecha de la publicación	Miembros de la familia de patentes	Fecha de la publicación
EP 1344776 A	*17.09.2003*	*NINGUNO*	
WO 2005003098 A1	*13.01.2005*	*AU 2004254205 A1*	*13.01.2005*
		BR PI0412231 A	*22.08.2006*
		CA 2531060 A1	*13.01.2005*
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		KR 20060027376 A	*27.03.2006*
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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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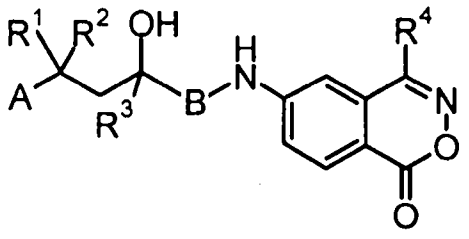
(54) Title: NON-STEROIDAL PROGESTERONE RECEPTOR MODULATORS



(I)

(57) Abstract: The present invention relates to non-steroidal progesterone receptor modulators of the general formula (I), a process for their preparation, the use of the progesterone receptor modulators for producing medicaments, and pharmaceutical compositions comprising these compounds. The compounds according to the invention are suitable for the therapy and prophylaxis of gynaecological disorders such as endometriosis, leiomyomas of the uterus, dysfunctional (bleeding)and dysmenorrhoea, and for the therapy and prophylaxis of hormone-dependent tumours and for use for female fertility control and for hormone replacement therapy.

WO 2006/136461 A3

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A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/12 C07D265/02 A61K31/536 A61P5/34

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, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 344 776 A (SCHERING AG [DE]) 17 September 2003 (2003-09-17) Abstract; paragraphs [0001]-[0010]; claims; examples. -----	1-25
A	WO 2005/003098 A1 (SCHERING AG [DE]) 13 January 2005 (2005-01-13)	1-25
X	Abstract; page 1; claims; examples. -----	26
X	DATABASE BEILSTEIN Beilstein Institut zur Förderung der Wissenschaften, Frankfurt/Main, DE; XP002406053 Database accession no. 1735553, 1964392, 2329868, 3529064 (RID). the whole document & J. PHARM.SCI., vol. 82, no. 6, 1993, pages 605-609, -----	26
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
7 November 2006	22/11/2006

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	Weisbrod, Thomas

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/006531

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE BEILSTEIN Beilstein Institut zur Förderung der Wissenschaften, Frankfurt/Main, DE; XP002406062 Database accession no. 2214047 (RID) the whole document & J. CHEM. SOC. CHEM. COMMUN., vol. 4, 1990, pages 294-296, -----	26
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X	DATABASE BEILSTEIN Beilstein Institut zur Förderung der Wissenschaften, Frankfurt/Main, DE; XP002406064 Database accession no. 9573837 (RID) the whole document & BIOORG. MED. CHEM., vol. 11, no. 18, 2003, pages 4133-4142, -----	26
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2006/006531

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1344776 A	17-09-2003	NONE	
WO 2005003098 A1	13-01-2005	AU 2004254205 A1	13-01-2005
		BR PI0412231 A	22-08-2006
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		EP 1638945 A1	29-03-2006
		KR 20060027376 A	27-03-2006
		MX PA06000169 A	27-04-2006

459

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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Act: 411 PRESENTACION Folios: 458

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE PCT

PATENTE DE INVENCION [x] MODELO DE UTILIDAD [ ]

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Claudia M Nieva Cortes
Firma Responsable

Fecha_____

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