04 105799

Industria y Comercio

SUPERINTENDENCIA

Q.F.

Delegatura de Propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCION

21. **EXPEDIENTE No.** 04-105799

54. **TITULO** MIMETICOS DE GLUCOCORTICOIDES, PROCEDIMIENTOS PARA SU PREPARACION, COMPOSICIONES FARMACEUTICAS Y USOS DE LOS MISMOS

51. **CLASIFICACION INTERNACIONAL** A61K 31/44

71. **SOLICITANTE** BOEHRINGER INGELHEIM PHARMACEUTICALS, INC

DOMICILIO Ridgefield, Connecticut, Estados Unidos de América.

74. **APODERADO** EMILIO FERRERO

C.C. 438.019 de Usaquén.

22. **BOGOTA, D.C.,**

(FORMA P-10)

Industria y Comercio
SUPERINTENDENCIA

PETITORIO

SUPERINDUSTRIA Y COMERCIO
Radicacion : 04105799 00000000 Folios: 579 ión
Fecha (AMD): 2004-10-21 16:54:58
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO UNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.
☐ Capítulo I. ☒ Capítulo II.

2 SOLICITANTE (71)

Nombre: **BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.**
sociedad constituida y existente bajo las leyes del estado de Delaware, Estados Unidos de América.
Dirección: 900 Ridgebury Road,
P.O. Box 368, Ridgefield,
Connecticut 06877-0368,
Estados Unidos de América
Domicilio: Ridgefield, Connecticut,
Estados Unidos de América

IDENTIFICACIÓN

C.C. ☐ NIT ☐
C.E. ☐ Otro ☐
Cual ____
Número ____

3 REPRESENTANTE O APODERADO

Nombre: EMILIO FERRERO
Dirección: Carrera 4ª. No. 72-35
Teléfono: 347 35 11
Fax: 211 85 50
E-mail: clientes@camvp.com.
Domicilio: Bogotá, Colombia.

IDENTIFICACIÓN

C.C. ☒ NIT ☐
C.E. ☐ Otro ☐
Cual ____
Número 438.019 T.P 31.929

4 INVENTOR (ES) (72)

1. Younes BEKKALI
Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road, P.O. Box 368, Ridgefield, Connecticut 06877-0368, Estados Unidos de América

2. Raj BETAGERI
Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road, P.O. Box 368, Ridgefield, Connecticut 06877-0368, Estados Unidos de América

3. Thomas A. GILMORE
12 Andover Street, Salem, Massachusetts 01970, Estados Unidos de América.

4. Mario G. CARDOZO
579 Miramar Avenue, San Francisco, California 94112, Estados Unidos de América.

5. Thomas M. KIRRANE
Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road, P.O. Box 368, Ridgefield, Connecticut 06877-0368, Estados Unidos de América

6. Daniel KUZMICH
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7. John Robert PROUDFOOT
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8. Hidenori TAKAHASHI
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9. David THOMSON
Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road, P.O. Box 368, Ridgefield, Connecticut 06877-0368, Estados Unidos de América

10. Ji WANG
Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road, P.O. Box 368, Ridgefield, Connecticut 06877-0368, Estados Unidos de América

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

11. Renee ZINDELL
Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road, P.O. Box 368, Ridgefield, Connecticut 06877-0368, Estados Unidos de América

12. Christian Hanke Justus Joachim HARCKEN
Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road, P.O. Box 368, Ridgefield, Connecticut 06877-0368, Estados Unidos de América

13. Doris RIETHER
Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road, P.O. Box 368, Ridgefield, Connecticut 06877-0368, Estados Unidos de América

5 **PCT (86)**

Solicitud Internacional No. PCT/US03/08901 Fecha: 21 de Marzo de 2003

Publicación Internacional No. WO 03/082280 A1 Fecha: 9 de Octubre de 2003

6 **Título (54)**

MIMÉTICOS DE GLUCOCORTICOIDES, PROCEDIMIENTOS PARA SU PREPARACIÓN, COMPOSICIONES FARMACÉUTICAS Y USOS DE LOS MISMOS

7 **Clasificación Internacional (51)** A61K 31/44

8 **Prioridad** SI☒ NO☐

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	26 de Marzo de 2002	60/367.758
US	9 de Diciembre de 2002	60/431.817
US	24 de Enero de 2003	60/442.404

9 **Comprobante de pago No.:** 04 – 77.850 **Fecha:** 4 de Octubre de 2004

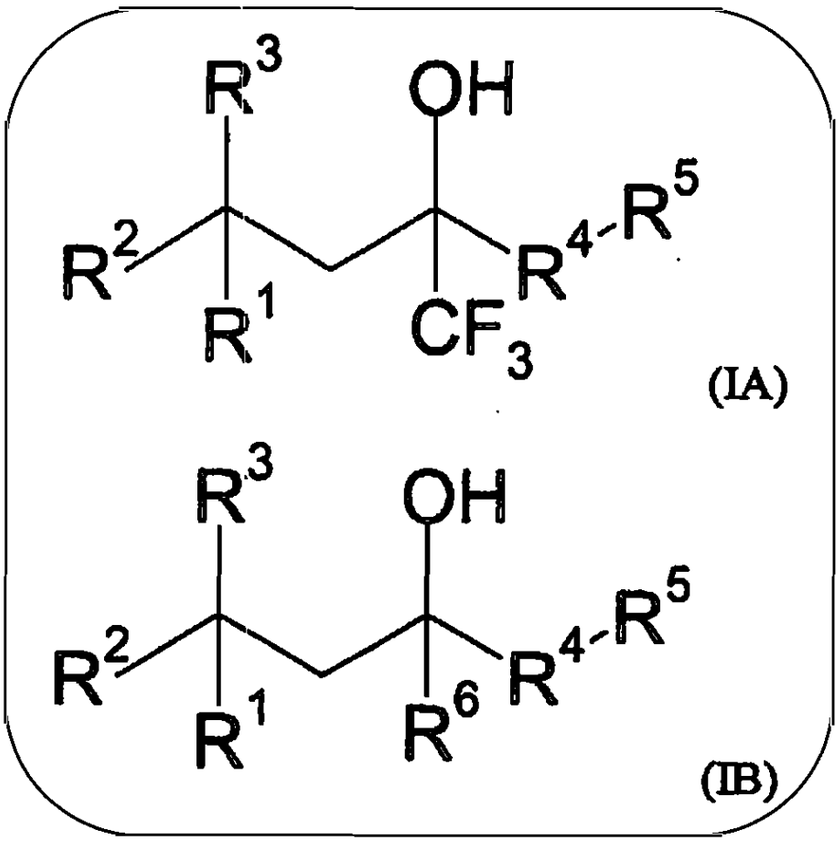
10

Anexos:

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por $ 422.000.oo.
- ☐ Comprobante de pago por reivindicación de prioridad.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar efectuado por la IPEA.
- ☒ Traducción del examen preliminar 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 12x12
- ☐ 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.
- ☐ Otros

11

FIGURA CARACTERÍSTICA



12 Solicito la concesión de la patente,

NOMBRE: EMILIO FERRERO

FIRMA : _____

C.C. 438.019 de Usaquén T.P. 31.929

PRP

CAVELIER
ABOGADOS
EDIFICIO SIUKI
CARRERA 7ª Nº 72-35
BOGOTA, 8 - COLOMBIA

07612
0569

For patents, utility models, industrial designs, trademarks, commercial names, trade emblems, slogans.

Para patentes, modelos de utilidad, diseños industriales, marcas de fábrica, nombres comerciales, enseñas, lemas comerciales.

REPRESENTACION Y PODER

REPRESENTATION AND POWER OF ATTORNEY

I (we), the undersigned/Yo (nosotros), abajo firmado (s)
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

of/domiciliado (s) en 900 Ridgebury Road,
Ridgefield, Connecticut 06877, United
States of America,

por el presente nombramos a GERMAN CAVELIER, tpa. 832; GONZALO PERDOMO, tpa. 831; EMILIO FERRERO, tpa. 31929; y LUZ CLEMENCIA DE PAEZ, tpa. 23555; domiciliados en la Carrera 4ª Nº 72-35, Bogotá, Colombia, en obedecimiento a lo dispuesto en el parágrafo 1º del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como mis (nuestros) representantes en todos los asuntos de propiedad industrial con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo de aquél. La misma regla se aplicará cuando el segundo representante suplente haya de reemplazar al primero, o el tercero al segundo. En tales casos, el representante principal, o el primero, o segundo suplente, en su caso, o ambos, declararán su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario u otro Funcionario Público, o Cónsul de Colombia, en el extranjero; y si se tratare de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare definitivamente, el siguiente tomará su lugar. Cuando cesare la ausencia o impedimento del representante principal, o de su primero o segundo suplentes, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndola por el solo hecho de ejercerla, cesando en ese momento el ejercicio de la representación por el primero, segundo o tercer suplente en su caso.

Además, confiero (conferimos) poder a los abogados arriba nombrados, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad y diseños industriales; el registro de marcas de fábrica, colectivas, defensivas, de servicio, lemas comerciales, nombres comerciales, enseñas, variedades vegetales y denominaciones de origen; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Las acciones de competencia desleal, protección del consumidor, oposiciones u observaciones, cancelación administrativa y judicial, nulidad, medidas cautelares, concesión de licencias, la tutela, la protección de secretos industriales, y en general los juicios civiles, penales, administrativos o contencioso-administrativos relacionados con estos derechos; acciones y procesos que promovamos o se nos promuevan. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

in due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint GERMAN CAVELIER, tpa. 832; GONZALO PERDOMO, tpa. 831; EMILIO FERRERO, tpa. 31929; and LUZ CLEMENCIA DE PAEZ, tpa. 23555; domiciled at Carrera 4ª Nº 72-35, Bogotá, Colombia, the first as principal and the others as alternates, in the order of their appointment, as our representatives for all industrial property matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporal or definitive impediment. The same rule will apply when the second alternate representative is to replace the first one, or when the third is to replace the first or second alternates in their turn, or both of them, second. In such cases, the principal representative, or the first or second alternates in their turn, or both of them, shall state their intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombian Consul abroad; and in case of impediment, the appropriate certificate shall suffice. If any of the appointees were to be definitely absent, the following alternate shall take his place. When the absence or impediment of the principal representative, or of the first or second alternate in their turn ceases, the representation can be taken again in their sequence, by the principal, the first or second alternate depending on case, and the mere fact or its exercise will suffice. The exercise of the representation by the first, second or third alternates in their turn shall end at such time.

In addition, we grant a Power of Attorney in favor of the above-named attorneys-at-law so that they may obtain the protection of my (our) industrial property and against the unfair competition for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models and industrial designs; the registration of trademarks, collective, defensive and service marks, slogans, commercial names, trade emblems, vegetal varieties and denominations of origin; its renewal, assignment, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b) Actions of unfair competition, protection to the consumer, oppositions or observations, administrative or Court cancellation, nullity, infringement, granting of licenses, the action for writ mandamus, the protection of trade secrets, and in general the civil, penal, and administrative suits relating to those rights; actions and suits instituted by me (us) or against me (us). And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

Given and signed this/Dado y firmado hoy 29th
day of August, 1996
in/en Ridgefield, Connecticut USA

Signature Firma
Dr. Robert P. Raymond
Chief Patent Counsel
Boehringer Ingelheim Pharmaceuticals, Inc.

96912.
ANA MARIA SALVETTI
TRADUCTORA E INTERPRETE OFICIAL
INGLES - ITALIANO - ESPAÑOL
DTE. No. 158 M. JUSTICIA

© CAVELIER ABOGADOS

9/087

CERTIFICADO NOTARIAL (INDIVIDUO)

A los 29 días del mes de AGOSTO de 19 96

ante mí, Notario Público de Connecticut, EE.UU.

compareció(eron) personalmente Dr. Robert P. Raymond

a quien(es) doy fe de conocer y me consta que es(son) la(s) persona(s) firmante(s) del documento que precede, y quien(es) tiene(n) capacidad legal para otorgarlo.

MARY-ELLEN M. DEVLIN
NOTARY PUBLIC
MY COMMISSION EXPIRES OCT. 31, 2000

Notario Público — Notary Public

NOTARIAL CERTIFICATE (INDIVIDUAL)

On this 29 day of August 19 96

before me, a Notary Public of Connecticut, USA

personally appeared Dr. Robert P. Raymond

to me known, and known to me to be the person(s) who executed that foregoing document, and who has(have) legal capacity to execute it.

Mary-Ellen M. Devlin
My Commission Expires 10/31/2000

CERTIFICADO NOTARIAL (SOCIEDAD)

Hoy, 29 de Agosto de 19 96

compareció(eron) ante mí
Dr. Robert P. Raymond

a quien(es) conozco personalmente y que firma(n) este documento en representación de la Sociedad/compañía

denominada BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

Certifico:

1. Que he visto los siguientes documentos:*

ESCRITURA DE LA SOCIEDAD, ESTATUTOS Y VARIOS RESOLUCIONES DE LA JUNTA DIRECTIVA , BIL-071 de fecha 29 de noviembre de 1984.

2. Que dichos documentos prueban lo siguiente:

2.1. Que BOEHRINGER INGELHEIM PHARMACEUTICALS, INC. es una Sociedad/Compañía legalmente constituída y existente de acuerdo con las leyes de l Estado de Delaware, Estados Unidos de América

COMO NOTARIO DEL ESTADO DE CHILE
JUAN MANUEL BOTERO MEDINA
19 OCT 2004

2.2. Que el domicilio de dicha Sociedad/Compañía es 900 Ridgebury Road, Ridgefield, Connecticut 06877, Estados Unidos de América

2.3. Que el objeto u objeto para los cuales se otorga el presente poder están comprendidos dentro del objeto social de la mencionada Sociedad/Compañía.

2.4. Que el(los) Sr.(Sres.) DR. ROBERT P. RAYMOND

está(n) autorizado(s) para otorgar el presente Poder.

Ciudad Ridgefield
Estado Connecticut, EE.UU.
Hoy 29 Agosto de 19 96

NOTARIAL CERTIFICATE (CORPORATION)

On this 29 day of August 19 96

appeared before me

Dr. Robert P. Raymond

who(m) I know personally and who(m) signed this document as representative(s) of the Corporation/Company

named BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

I Certify:

1. That I have seen the following documents:*

Corporate Charter, By-Laws and various, board resolutions, BIL-071 dated November 29, 1984.

2. That the above documents duly prove the following:

2.1. That BOEHRINGER INGELHEIM PHARMACEUTICALS, INC. is a Corporation/Company legally constituted and in existence in accordance with the laws of the State of Delaware, United States of America

2.2. That the domicile of said Corporation/Company is 900 Ridgebury Road, Ridgefield, Connecticut 06877, United States of America

2.3. That the purpose of purposes for which the preset Power of Attorney is granted are comprised within the corporation purposes set forth in the charter of the mentioned Corporation/Company.

2.4. That Mr.(Messrs.) Dr. Robert P. Raymond

is(are) authorized to grant the present Power of Attorney.

City Ridgefield
State Connecticut, USA
This 29th day of August 19 96

MARY-ELLEN M. DEVLIN
NOTARY PUBLIC
MY COMMISSION EXPIRES OCT. 31, 2000

Notario Público — Notary Public

* Los documentos deben identificarse con fecha y origen.

* Documents muts be identified with date and origin.

(0404/07/T/Rev. 11-92)

5

STATE OF CONNECTICUT
OFFICE OF THE SECRETARY OF THE STATE

I, **MILES S. RAPOPORT**, Secretary of the State of Connecticut, and keeper of the seal thereof,

DO HEREBY CERTIFY: that BARBARA SERFILIPPI was duly elected or appointed to the office of TOWN CLERK for the town of RIDGEFIELD in the County of FAIRFIELD in said State, for the term of JANUARY 1, 1996 to JANUARY 5, 1998;

and that to his/her acts and attestations as such, full faith and credit are and ought to be given in and out of Court.

In Testimony Whereof, I have hereunto set my hand and affixed the Great Seal of the State of Connecticut, at Hartford, on August 30, 1996.

Miles S. Rapoport
Secretary of the State

96912.
ANA MARIA SALVETTI
TRADUCTORA E INTERPRETE OFICIAL
INGLES - ITALIANO - ESPAÑOL
DES. No 158 MINJUSTICIA

CONO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
19 OCT 2004
MANUEL BOTERO MEDINA
NOTARIO

STATE OF CONNECTICUT
COUNTY OF FAIRFIELD } ss. RIDGEFIELD

I, Barbara Serfilippi, Clerk of the Town of Ridgefield in said County, do hereby certify that Mary Ellen M. Devlin by and before whom the foregoing (or annexed) acknowledgment was taken, was at the time of taking the same a notary public (or other officer) residing (or authorized to act) in said County, and was authorized by the laws of said State to take and certify acknowledgments in said State, and, further, that I believe that the signature to the certificate of acknowledgment is genuine.

IN TESTIMONY WHEREOF, I have hereunto set my hand and affixed the seal of the State and Town this 29th day of August 19 96.

96912
ANA MARIA SALVETTI
TRADUCTORA E INTERPRETE OFICIAL
INGLES - ITALIANO - ESPAÑOL
DES. No. 158 MINJUSTICIA

Barbara Serfilippi
Town Clerk

ADMS FORM 223

6

CONSULADO DE COLOMBIA

535 Boylston Street 11th Floor Boston, MA 02116 Tel: (617)536-6222 Fax: (617)536-9372

No 1156

El suscrito Cónsul de Colombia en Boston, MA, Estados Unidos vistos los documentos presentados

CERTIFICA:

Que el señor(a) **MILES S RAPOPORT**, quien autenticó la firma de **BARBARA SERFILIPPI**, secretario de la ciudad de Ridgefield, Connecticut, en el documento adjunto ejercía en la fecha allí indicada las funciones de **SECRETARIO DE ESTADO DEL ESTADO DE CONNECTICUT, USA** y su firma y sello son los que acostumbra a usar en sus actos oficiales. Que la compañía **BOEHRINGER INGELHEIM FARMACEUTICALS INC.**, con domicilio principal en la ciudad de **RIDGEFIELD, CONNECTICUT**, es sociedad constituida bajo las leyes del estado de **DELAWARE**, Estados Unidos y tienen y ejerce su objeto social conforme a las leyes de ese país. Que el señor **ROBERT P RAYMOND** en su calidad de **CONSEJERO JEFE DE PATENTES** de dicha compania esta debidamente autorizado para otorgar este poder a nombre de estas companias y, para los fines y propositos alli expresados.

La presente certificación se expide en cumplimiento del artículo 480 del Código de Comercio.

El Cónsul no asume responsabilidad por el contenido del documento.

Esta certificación se expide en Boston a los 13 días del mes de Septiembre de 1996

Pagado Impuesto de Timbre US$6.00

LUIS FERNANDO LEMAITRE
VICECONSUL

CONSULADO DE COLOMBIA BOSTON

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

19 OCT 2004

JUAN MANUEL BOTERO MEDINA
NOTARIO

96912

ANA MARIA SALVETTI
TRADUCTORA E INTERPRETE OFICIAL
INGLES - ITALIANO - ESPAÑOL
RES. No. 158 MINJUSTICIA

MINISTERIO DE RELACIONES EXTERIORES

NO SE ASUME RESPONSABILIDAD DEL TEXTO

1996 SET 25 A 11: 45

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C

JUAN MANUEL GUTIÉRREZ MEDINA
NOTARIO

19 OCT 2004

MINISTERIO DE RELACIONES EXTERIORES

NO SE ASUME RESPONSABILIDAD DEL TEXTO

1996 SET 25 A 11: 45

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C

CERTIFICACION NOTARIAL Y AUTENTICACION CONSULAR

1. Es necesaria la legalización con certificado notarial. El Notario Público debe certificar:

1.1. Que la compañía está legalmente constituída y actualmente existente.

1.2. Su domicilio.

1.3. Que el propósito del poder está incluído en el objeto social de la compañía.

1.4. Que el poderdante está autorizado para dar el poder en nombre de la compañía.

2. Los documentos que hay que mostrarle al Notario Público para probar los puntos anteriores, deben estar expresados en el Certificado Notarial con fecha y origen:

2.1. Respecto a los puntos 1.1, 1.2 y 1.3 sugerimos referirse a los artículos de constitución con fecha y lugar de otorgamiento; y

2.2. Para el punto 1.4 sugerimos mencionar la resolución de la Junta Directiva o los estatutos, según los cuales la persona que otorga el poder está autorizada para ello.

3. Enseguida el Señor Cónsul de Colombia debe autenticar la firma del Notario Público.

NOTARIAL CERTIFICATION AND CONSULAR AUTENTIFICATION

1. Notarial legalization is necessary. The Notary Public must certify:

1.1. That the company is legally constituted and presently existent.

1.2. Its place of business.

1.3. That the purpose of the Power-of-Attorney is included in the activities of the company.

1.4. That the grantor is empowered to give the Power of Attorney in the name of the company he represents.

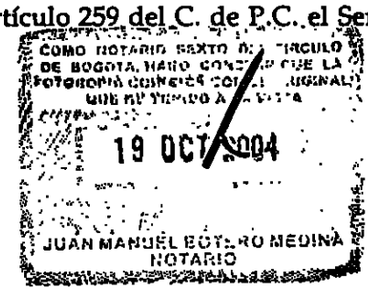
2. The documents which the Notary Public had before him to prove the above points must be listed by him in the Notarial Certificate with dated and origin:

2.1. In connection with points 1.1., 1.2. and 1.3 we suggest referring to the articles of incorporation with date and place of execution.

2.2. For point 1.4 we suggest to mention the resolution of the Board of Directors and/or the by-laws whereby the person who grants the Power of Attorney has been authorized to give it.

3. Then the Colombian Consul must legalize the signature of the Notary Public.

NOTA PARA EL SEÑOR CONSUL COLOMBIANO: Según el artículo 259 del C. de P.C. el Señor Cónsul debe autenticar la última precedente autenticación.



TRADUCCION OFICIAL No.96912 de un documento escrito en inglés, el cual para su identificación se sella con el sello del Traductor al mismo tiempo que la presente. Esta Traducción ha sido preparada por Ana María Salvetti, Traductora Oficial debidamente reconocida por el Ministerio de Relaciones Exteriores y aprobada por el Ministerio de Justicia colombiano mediante Resolución No.158 de 1991.

(Se traducen sellos y legalizaciones que aparecen a continuación de un poder escrito en inglés y español, otorgado por la sociedad **BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.**, a favor de Germán CAVELIER, Gonzalo PERDOMO, Emilio FERRERO, y Luz Clemencia de PAEZ.)

Dado y firmado el 29 de agosto de 1996 en Ridgefield, Connecticut EE.UU. (Firmado), ilegible, Robert P. Raymond, Principal Asesor de Patentes. Boehringer Ingelheim Pharmaceuticals, Inc.

(en inglés y español): CERTIFICACION NOTARIAL (INDIVIDUO) referente a la firma que antecede. (Firmado), Marry-Ellen M. Devlin, Notario Público. Mi comisión expira el 31 de octubre del 2000. Sello seco del Notario.

CERTIFICACION NOTARIAL (SOCIEDAD) referente a la existencia y representación de la sociedad mencionada. (Firmado), Mary-Ellen M. Devlin, Notario Público. Mi comisión expira el 31 de octubre del 2000. Sello seco del Notario.

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

19 OCT 2004

JUAN MANUEL ROJAS GUARDIOLA

ESTADO DE CONNECTICUT

CONDADO DE FAIRFIELD, ss. RIDGEFIELD

Yo, Barbara Serfilippi, Escribano de la Población de

Ridgefield, en dicho Condado, por medio del presente certifico que Mary Ellen M. Devlin, por y ante quien el anterior reconocimiento (o adjunto) fue tomado, era al momento de tomarlo, un Notario Público (u otro funcionario) domiciliado (o autorizado para actuar) en dicho Condado, y que estaba autorizado por las leyes de dicho Estado para tomar y certificar reconocimientos en dicho Estado, y además, que creo que la firma que aparece en el certificado de reconocimiento es auténtica.

En Testimonio de lo Cual, he firmado y estampado del sello del Esado y Población hoy, 29 de agosto de 1996. (Firmado), Barbara Serfilippi, Escribano.

(0404/07/T/Rev.11-92)

ESTADO DE CONNECTICUT

OFICINA DEL SECRETARIO DEL ESTADO

Yo, Miles S. Rapoport, Secretario del Estado de Connecticut, y guardián de su Sello, POR MEDIO DEL PRESENTE CERTIFICO que BARBARA SERFILIPPI fue debidamente elegida o nombrada para el cargo de ESCRIBANO DEL CONDADO para la población de RIDGEFIELD en el Condado de FAIRFIELD en dicho Estado, para el período que va del lo. de enero de 1996 al 5 de enero de 1998 y que sus actos oficiales en calidad de tal merecen completa fe y crédito dentro y fuera de la Corte. En testimonio de lo cual, he firmado y estampado el Gran Sello del Estado de Connecticut, en Hartford, el 30 de agosto de 1996. (Firma facsimilar), Miles S. Rapoport, Secretario del Estado. Adherido se encuentra sello de oblea del Estado de Connecticut. Sello seco del Consulado de Colombia en Boston,

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA CORRESPONDE FIELMENTE AL ORIGINAL QUE HE TENIDO A LA VISTA

JUAN MANUEL BOTERO MEDINA
NOTARIO

EE.UU.

(en español): **Certificación No.1156** del 13 de septiembre de 1996, de la firma que antecede por el Consulado de Colombia en Boston. Pagados impuesto de timbre y derechos de fondo rotatorio. (Firmado), Luis Fernando Lemaitre, Cónsul. Sello consular en tinta. **Certificación No.213241** del 24 de septiembre de 1996 de la firma que antecede por el Ministerio de Relaciones Exteriores. (Firmado), Jefe Legalizaciones.

Es traducción fiel y completa de la cual se deja copia en los archivos de esta oficina para su confrontación y a la cual me remito.

Santa fe de Bogotá, 30 de septiembre de 1996

COLO-7612-801-005-5

ams/~~59~~-60

COMO NOTARIO SEXTO ENCARGADO DE SANTAFE DE BOGOTA HAGO CONSTAR QUE LA FIRMA DE

C. C.

COINCIDE CON LA REGISTRADA POR EL (ELLA) EN ESTA NOTARIA.

30 SET. 1996

SANTAFE D BOGOTA, D.C.

ANA MARIA CALVETTI
TRADUCTORA E INTERPRETE OFICIAL
INGLES - ITALIANO - ESPAÑOL
RES. No. 158 MINJUSTICIA

COMO NOTARIO SEXTO ENCARGADO DE SANTAFE DE BOGOTA D.C. FOTOCOPIA CONCUERDA CON EL ORIGINAL QUE HE TENIDO A LA VISTA

19 OCT 2004

JUAN MANUEL BOTERO MEDINA
NOTARIO

MINISTERIO DE RELACIONES EXTERIORES
Ana María
263981

CUYA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.
30 SET 12:07

NO SE ASUME RESPONSABILIDAD DEL TEXTO

NOTARIA SEXTA
J. B. C. FERNANDEZ
Notario Sexto Encargado

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TELEFONO: (57) (1) 2120100

11

Señor Jefe de la
DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Poderdante: BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

Poder conferido el: 29-08-96

Yo, GERMAN CAVELIER, obrando en mi calidad de apoderado principal del poderdante arriba mencionado, atentamente manifiesto a Usted que sustituyo el poder que me ha sido conferido en la persona del doctor EMILIO FERRERO, Abogado con Tarjeta Profesional No. 31.929, con todas las facultades que me fueron conferidas.

COPIA FOTOCOPIA CONCIDE CON EL ORIGINAL
19 OCT 2004
NOTARIO

Hago la anterior sustitución conforme al artículo 66 del Código de Procedimiento Civil ya que los otros sustitutos faltan en este momento.

Señor Jefe,

GERMAN CAVELIER
T.P.A. No. 832
C.C. No. 2.877.924 de Bogotá

Acepto:

EMILIO FERRERO
T.P.A. Nº 31.929
C.C. No. 438.019 de Usaquén

2e-780-2

NOTARIA SEXTA DE BOGOTA

RECONOCIMIENTO Y PRESENTACION PERSONAL

Santafé de Bogotá D. C. 06 SET 1996

Ante Mí JUAN MANUEL BOTERO MEDINA

NOTARIO SEXTO DEL CIRCULO DE BOGOTA

Compareció(eron) personalmente,

quien(es) exhibió(eron) la(s) C. 4

y la(s) Libreta(s) Militar(es).

domiciliado(s) en S , y a[illegible] que la(s) firma(s) que aparece(n) en el p[illegible] es(son) la(s) suya(s), y que el contenido de[illegible]

En constancia se firma esta diligencia.

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

19 OCT 2004

JUAN MANUEL BOTERO MEDINA
NOTARIO

REPUBLICA DE COLOMBIA
Juan Manuel Botero Medina
Notario Sexto
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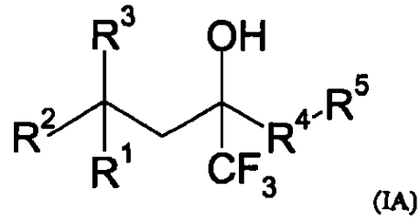
(74) Agents: **RAYMOND, Robert, P.** et al.; Boehringer Ingelheim Corporation, 900 Ridgebury Road, P.O. Box 368, Ridgefield, CT 06877-0368 (US).

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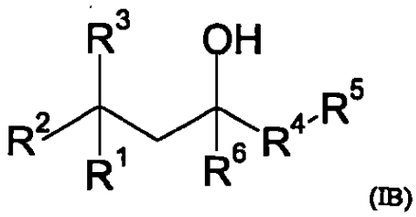
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[Continued on next page]

(54) Title: GLUCOCORTICOID MIMETICS, METHODS OF MAKING THEM, PHARMACEUTICAL COMPOSITIONS, AND USES THEREOF



(IA)



(IB)

(57) Abstract: Compounds of Formula (IA) and Formula (IB) wherein R^1, R^2, R^3, R^4, R^5 and R^6 are as defined herein for Formula (IA) or Formula (IB), or a tautomer, prodrug, solvate, or salt thereof; pharmaceutical compositions containing such compounds, and methods of modulating the glucocorticoid receptor function and methods of treating disease-states or conditions mediated by the glucocorticoid receptor function or characterized by inflammatory, allergic, or proliferative processes in a patient using these compounds.

WO 03/082280 A1

Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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

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GLUCOCORTICOID MIMETICS, METHODS OF MAKING THEM, PHARMACEUTICAL COMPOSITIONS, AND USES THEREOF

Field of the Invention

The present invention relates to glucocorticoid mimetics or ligands, methods of making such compounds, their use in pharmaceutical compositions, and their use in modulating the glucocorticoid receptor function, treating disease-states or conditions mediated by the glucocorticoid receptor function in a patient in need of such treatment, and other uses.

Background of the Invention

Glucocorticoids, a class of corticosteroids, are endogenous hormones with profound effects on the immune system and multiple organ systems. They suppress a variety of immune and inflammatory functions by inhibition of inflammatory cytokines such as IL-1, IL-2, IL-6, and TNF, inhibition of arachidonic acid metabolites including prostaglandins and leukotrienes, depletion of T-lymphocytes, and reduction of the expression of adhesion molecules on endothelial cells (P.J. Barnes, Clin. Sci., 1998, 94, pp. 557-572; P.J. Barnes *et al.*, Trends Pharmacol. Sci., 1993, 14, pp. 436-441). In addition to these effects, glucocorticoids stimulate glucose production in the liver and catabolism of proteins, play a role in electrolyte and water balance, reduce calcium absorption, and inhibit osteoblast function.

The anti-inflammatory and immune suppressive activities of endogenous glucocorticoids have stimulated the development of synthetic glucocorticoid derivatives including dexamethasone, prednisone, and prednisolone (L. Parente, Glucocorticoids, N.J. Goulding and R.J. Flowers (eds.), Boston: Birkhauser, 2001, pp. 35-54). These have found wide use in the treatment of inflammatory, immune, and allergic disorders including rheumatic diseases such as rheumatoid arthritis, juvenile arthritis, and ankylosing spondylitis, dermatological diseases including psoriasis and pemphigus, allergic disorders including allergic rhinitis, atopic dermatitis, and contact dermatitis, pulmonary conditions including asthma and chronic obstructive pulmonary disease (COPD), and other immune and inflammatory diseases including Crohn disease, ulcerative colitis, systemic lupus erythematosus, autoimmune chronic active hepatitis, osteoarthritis, tendonitis, and bursitis (J. Toogood, Glucocorticoids, N.J. Goulding and R.J. Flowers (eds.), Boston: Birkhauser, 2001, pp. 161-174). They have also been used to help prevent rejection in organ transplantation.

Unfortunately, in addition to the desired therapeutic effects of glucocorticoids, their use is associated with a number of adverse side effects, some of which can be severe and life-threatening. These include alterations in fluid and electrolyte balance, edema, weight gain, hypertension, muscle weakness, development or aggravation of diabetes mellitus, and osteoporosis. Therefore, a compound that exhibited a reduced side effect profile while maintaining the potent anti-inflammatory effects would be particularly desirable especially when treating a chronic disease.

The effects of glucocorticoids are mediated at the cellular level by the glucocorticoid receptor (R.H. Oakley and J. Cidlowski, Glucocorticoids, N.J. Goulding and R.J. Flowers (eds.), Boston: Birkhauser, 2001, pp. 55-80). The glucocorticoid receptor is a member of a class of structurally related intracellular receptors that when coupled with a ligand can function as a transcription factor that affects gene expression (R.M. Evans, Science, 1988, 240, pp. 889-895). Other members of the family of steroid receptors include the mineralocorticoid, progesterone, estrogen, and androgen receptors. In addition to the effects mentioned above for glucocorticoids, hormones that act on this receptor family have a profound influence on body homeostasis, mineral metabolism, the stress response, and development of sexual characteristics. Glucocorticoids, N.J. Goulding and R.J. Flowers (eds.), Boston: Birkhauser, 2001, is hereby incorporated by reference in its entirety to better describe the state of the art.

A molecular mechanism which accounts for the beneficial anti-inflammatory effects and the undesired side effects has been proposed (e.g., S. Heck *et al.*, EMBO J, 1994, 17, pp. 4087-4095; H.M. Reichardt *et al.*, Cell, 1998, 93, pp. 531-541; F. Tronche *et al.*, Curr. Opin. in Genetics and Dev., 1998, 8, pp. 532-538). Many of the metabolic and cardiovascular side effects are thought to be the result of a process called transactivation. In transactivation, the translocation of the ligand-bound glucocorticoid receptor to the nucleus is followed by binding to glucocorticoid response elements (GREs) in the promoter region of side effect-associated genes, for example, phosphoenolpyruvate carboxy kinase (PEPCK), in the case of increased glucose production. The result is an increased transcription rate of these genes which is believed to result, ultimately, in the observed side effects. The anti-inflammatory effects are thought to be due to a process called transrepression. In general, transrepression is a process

independent of DNA binding that results from inhibition of NF-kB and AP-1-mediated pathways, leading to down regulation of many inflammatory and immune mediators. Additionally, it is believed that a number of the observed side effects may be due to the cross-reactivity of the currently available glucocorticoids with other steroid receptors, particularly the mineralocorticoid and progesterone receptors.

Thus, it may be possible to discover ligands for the glucocorticoid receptor that are highly selective and, upon binding, can dissociate the transactivation and transrepression pathways, providing therapeutic agents with a reduced side effect profile. Assay systems to determine effects on transactivation and transrepression have been described (e.g., C.M. Bamberger and H.M. Schulte, Eur. J. Clin. Invest., 2000, 30 (suppl. 3), pp. 6-9). Selectivity for the glucocorticoid receptor may be determined by comparing the binding affinity for this receptor with that of other steroid family receptors including those mentioned above.

Glucocorticoids also stimulate the production of glucose in the liver by a process called gluconeogenesis and it is believed that this process is mediated by transactivation events. Increased glucose production can exacerbate type II diabetes, therefore a compound that selectivity inhibited glucocorticoid mediated glucose production may have therapeutic utility in this indication (J.E. Freidman *et al.*, J. Biol. Chem., 1997, 272, pp. 31475-31481).

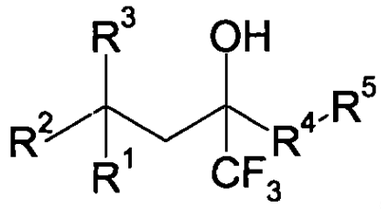
Novel ligands for the glucocorticoid receptor have been described in the scientific and patent literature. For example, PCT International Publication No. WO 99/33786 discloses triphenylpropanamide compounds with potential use in treating inflammatory diseases. PCT International Publication No. WO 00/66522 describes non-steroidal compounds as selective modulators of the glucocorticoid receptor potentially useful in treating metabolic and inflammatory diseases. PCT International Publication No. WO 99/41256 describes tetracyclic modulators of the glucocorticoid receptor potentially useful in treating immune, autoimmune, and inflammatory diseases. U.S. Patent No. 5,688,810 describes various non-steroidal compounds as modulators of glucocorticoid and other steroid receptors. PCT International Publication No. WO 99/63976 describes a non-steroidal, liver-selective glucocorticoid antagonist potentially useful in the treatment of diabetes. PCT International Publication No. WO 00/32584 discloses non-steroidal compounds having anti-inflammatory activity with

dissociation between anti-inflammatory and metabolic effects. PCT International Publication No. WO 98/54159 describes non-steroidal cyclically substituted acylanilides with mixed gestagen and androgen activity. U.S. Patent No. 4,880,839 describes acylanilides having progestational activity and EP 253503 discloses acylanilides with antiandrogenic properties. PCT International Publication No. WO 97/27852 describes amides that are inhibitors of farnesyl-protein transferase.

A compound that is found to interact with the glucocorticoid receptor in a binding assay could be an agonist or an antagonist. The agonist properties of the compound could be evaluated in the transactivation or transrepression assays described above. Given the efficacy demonstrated by available glucocorticoid drugs in inflammatory and immune diseases and their adverse side effects, there remains a need for novel glucocorticoid receptor agonists with selectivity over other members of the steroid receptor family and a dissociation of the transactivation and transrepression activities. Alternatively, the compound may be found to have antagonist activity. As mentioned above, glucocorticoids stimulate glucose production in the liver. Increased glucose production induced by glucocorticoid excess can exacerbate existing diabetes, or trigger latent diabetes. Thus a ligand for the glucocorticoid receptor that is found to be an antagonist may be useful, *inter alia*, for treating or preventing diabetes.

Summary of the Invention

The instant invention is directed to compounds of Formula (IA)



(IA)

wherein:

R^1 is an aryl or heteroaryl group, each optionally independently substituted with one to three substituent groups,

wherein each substituent group of R^1 is independently C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, C_3-C_8 cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_5 alkoxy, C_2-C_5

alkenyloxy, C_2-C_5 alkynyloxy, aryloxy, acyl, C_1-C_5 alkoxycarbonyl, C_1-C_5 alkanoyloxy, C_1-C_5 alkanoyl, aroyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, aminocarbonyloxy, C_1-C_5 alkylaminocarbonyloxy, C_1-C_5 dialkylaminocarbonyloxy, C_1-C_5 alkanoylamino, C_1-C_5 alkoxycarbonylamino, C_1-C_5 alkylsulfonylamino, aminosulfonyl, C_1-C_5 alkylaminosulfonyl, C_1-C_5 dialkylaminosulfonyl, halogen, hydroxy, carboxy, cyano, trifluoromethyl, trifluoromethoxy, nitro, or amino wherein the nitrogen atom is optionally independently mono- or di-substituted by C_1-C_5 alkyl or aryl; or ureido wherein either nitrogen atom is optionally independently substituted with C_1-C_5 alkyl; or C_1-C_5 alkylthio wherein the sulfur atom is optionally oxidized to a sulfoxide or sulfone,

wherein each substituent group of R^1 is optionally independently substituted with one to three substituent groups selected from methyl, methoxy, halogen, hydroxy, oxo, cyano, or amino,

R^2 and R^3 are each independently hydrogen or C_1-C_5 alkyl, or R^2 and R^3 together with the carbon atom they are commonly attached to form a C_3-C_8 spiro cycloalkyl ring;

R^4 is C_1-C_5 alkyl, C_2-C_5 alkenyl, or C_2-C_5 alkynyl, each optionally independently substituted with one to three substituent groups,

wherein each substituent group of R^4 is independently C_1-C_3 alkyl, hydroxy, halogen, amino, or oxo; and

R^5 is a heteroaryl group optionally independently substituted with one to three substituent groups,

wherein each substituent group of R^5 is independently C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, C_3-C_8 cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_5 alkoxy, C_2-C_5 alkenyloxy, C_2-C_5 alkynyloxy, aryloxy, acyl, C_1-C_5 alkoxycarbonyl, C_1-C_5 alkanoyloxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, aminocarbonyloxy, C_1-C_5 alkylaminocarbonyloxy, C_1-C_5 dialkylaminocarbonyloxy, C_1-C_5 alkanoylamino, C_1-C_5

alkoxycarbonylamino, C_1-C_5 alkylsulfonylamino, aminosulfonyl, C_1-C_5 alkylaminosulfonyl, C_1-C_5 dialkylaminosulfonyl, halogen, hydroxy, carboxy, cyano, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, nitro, or amino wherein the nitrogen atom is optionally independently mono- or di-substituted by C_1-C_5 alkyl; or ureido wherein either nitrogen atom is optionally independently substituted with C_1-C_5 alkyl; or C_1-C_5 alkylthio wherein the sulfur atom is optionally oxidized to a sulfoxide or sulfone,

wherein each substituent group of R^5 is optionally independently substituted with one to three substituent groups selected from C_1-C_3 alkyl, C_1-C_3 alkoxy, halogen, hydroxy, oxo, cyano, amino, or trifluoromethyl,

or a tautomer, prodrug, solvate, or salt thereof.

Another aspect of the invention includes compounds of Formula (IA), wherein:

R^1 is thienyl, phenyl, naphthyl, dihydrobenzofuranyl, benzofuranyl, chromanyl, dihydroindolyl, indolyl, dihydrobenzothienyl, benzothienyl, benzodioxolanyl, dihydrobenzoxazolyl, benzoxazolyl, benzisoxazolyl, benzpyrazolyl, benzimidazolyl, quinolinyl, pyridinyl, pyrimidinyl, or pyrazinyl, each optionally independently substituted with one to three substituent groups,

wherein each substituent group of R^1 is independently C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, C_1-C_3 alkoxy, C_2-C_3 alkenyloxy, C_1-C_3 alkanoyl, C_1-C_3 alkoxycarbonyl, C_1-C_3 alkanoyloxy, halogen, hydroxy, carboxy, cyano, trifluoromethyl, trifluoromethoxy, nitro, or C_1-C_3 alkylthio wherein the sulfur atom is optionally oxidized to a sulfoxide or sulfone,

wherein each substituent group of R^1 is optionally independently substituted with a substituent group selected from methyl, methoxy, halogen, hydroxy, oxo, cyano, or amino;

R^2 and R^3 are each independently hydrogen or C_1-C_3 alkyl, or R^2 and R^3 together with the carbon atom they are commonly attached to form a C_3-C_6 spiro cycloalkyl ring;

R^4 is CH_2; and

R^5 is an imidazolyl, pyridyl, indolyl, azaindolyl, diazaindolyl, benzofuranyl, furanopyridinyl, furanopyrimidinyl, benzothienyl, thienopyridinyl, thienopyrimidinyl, benzoxazolyl, oxazolopyridinyl, benzothiazolyl, thiazolopyridinyl, benzimidazolyl, imidazolopyridinyl, quinolinyl, or isoquinolinyl group, each optionally independently substituted with one to three substituent groups,

wherein each substituent group of R^5 is independently C_1-C_3 alkyl, C_2-C_3 alkenyl, phenyl, C_1-C_3 alkoxy, methoxycarbonyl, aminocarbonyl, C_1-C_3 alkylaminocarbonyl, C_1-C_3 dialkylaminocarbonyl, heterocyclylcarbonyl, fluoro, chloro, bromo, cyano, trifluoromethyl, or C_1-C_3 alkylthio wherein the sulfur atom is optionally oxidized to a sulfoxide or sulfone,

wherein each substituent group of R^5 is optionally independently substituted with a substituent group selected from methyl, methoxy, fluoro, chloro, bromo, oxo, or trifluoromethyl,

or a tautomer, prodrug, solvate, or salt thereof.

Yet another aspect of the invention includes compounds of Formula (IA), wherein:

R^1 is thienyl, phenyl, naphthyl, pyridyl, chromanyl, dihydrobenzofuranyl, or benzofuranyl, each optionally independently substituted with one or two substituent groups,

wherein each substituent group of R^1 is independently methyl, ethyl, methoxy, ethoxy, fluoro, chloro, bromo, hydroxy, trifluoromethyl, trifluoromethoxy, or cyano;

R^2 and R^3 are each independently methyl, or R^2 and R^3 together with the carbon atom they are commonly attached to form a spiro cyclopropyl ring;

R^4 is CH_2; and

R^5 is a pyridyl, indolyl, azaindolyl, benzofuranyl, furanopyridinyl, thienopyridinyl, benzoxazolyl, benzimidazolyl, quinolinyl, or isoquinolinyl group, each optionally independently substituted with one to three substituent groups,

wherein each substituent group of R^5 is independently methyl, phenyl, methoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, morpholinylcarbonyl, fluoro, chloro, bromo, cyano, or trifluoromethyl,

or a tautomer, prodrug, solvate, or salt thereof.

Yet another aspect of the invention includes compounds of Formula (IA), wherein:

R^1 is phenyl, dihydrobenzofuranyl, or benzofuranyl, each optionally independently substituted with one to three substituent groups,

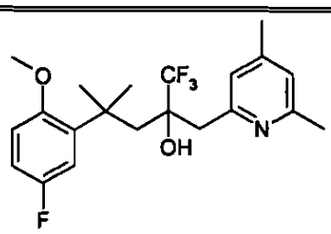
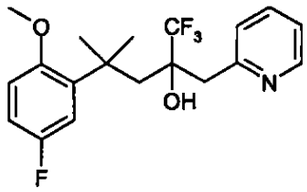
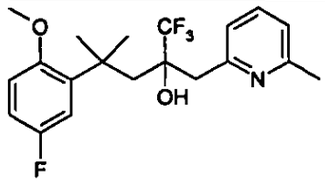
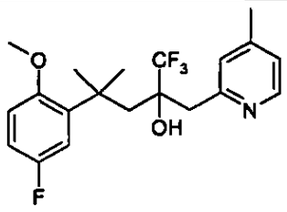
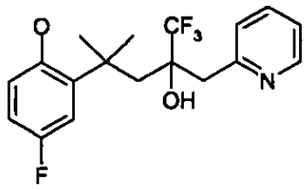
wherein each substituent group of R^1 is independently C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, C_1-C_3 alkoxy, C_2-C_3 alkenyloxy, C_1-C_3 alkanoyl, C_1-C_3 alkoxycarbonyl, C_1-C_3 alkanoyloxy, halogen, hydroxy, carboxy, cyano, trifluoromethyl, nitro, or C_1-C_3 alkylthio wherein the sulfur atom is optionally oxidized to a sulfoxide or sulfone; and

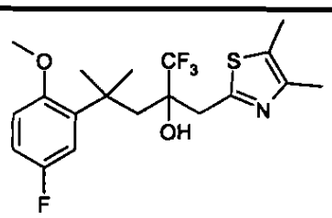
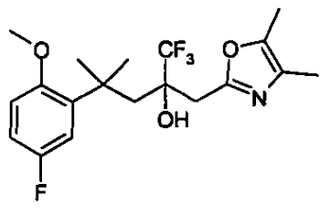
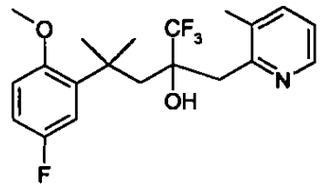
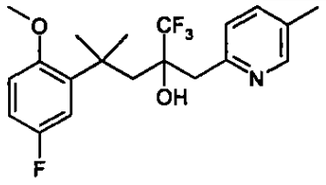
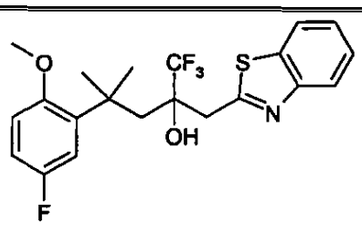
R^2 and R^3 are each independently hydrogen or C_1-C_3 alkyl,

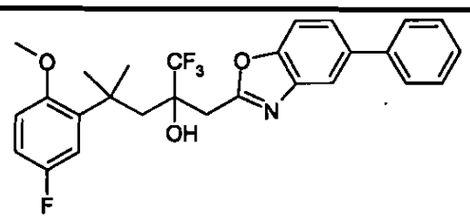
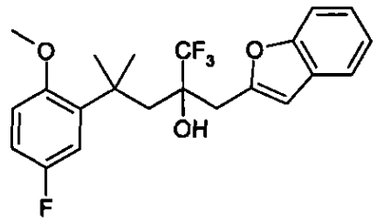
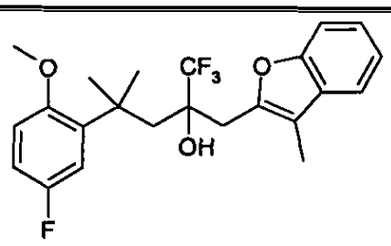
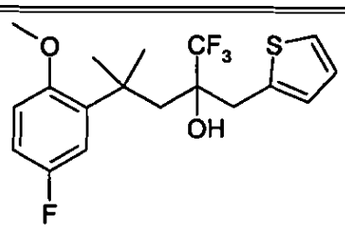
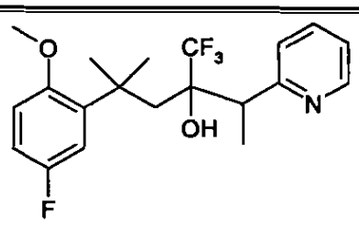
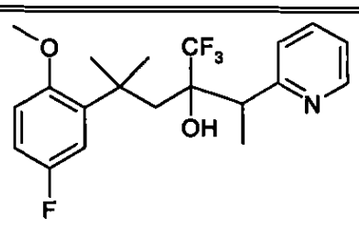
or a tautomer, prodrug, solvate, or salt thereof.

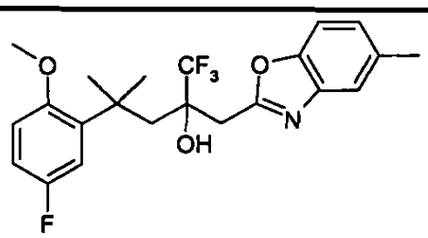
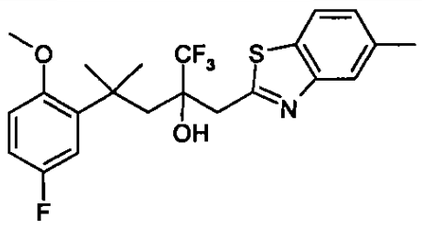
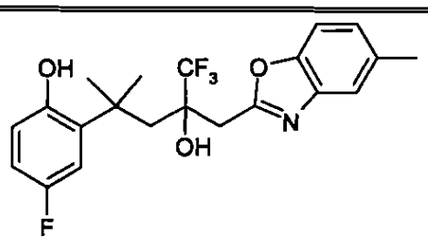
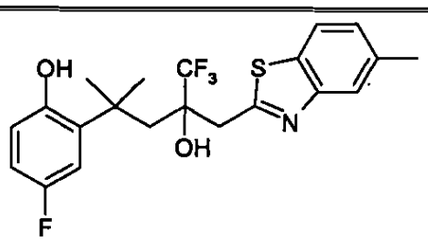
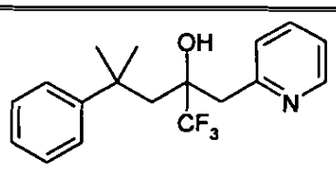
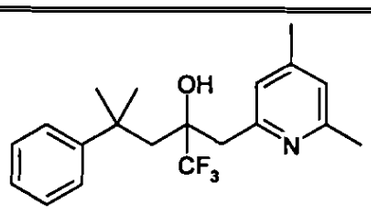
In yet other aspects of the invention, one to three substituent groups of R^1 in the compounds of Formula (IA) is independently C_1-C_3 alkylamino or C_1-C_3 dialkylamino.

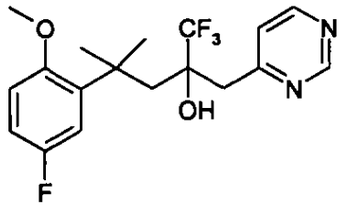
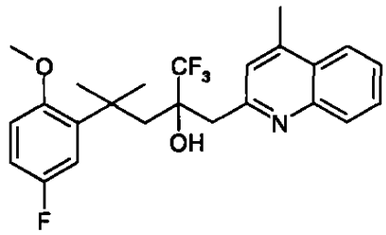
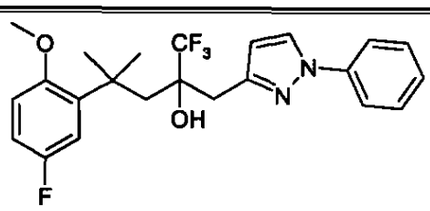
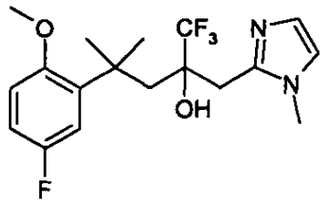
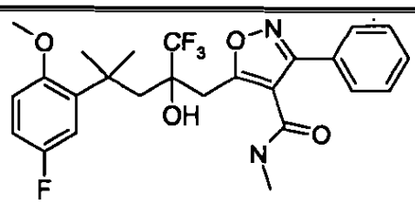
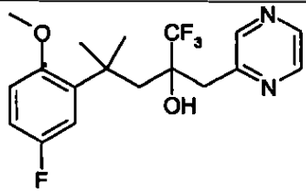
The following are representative compounds of Formula (IA) according to the invention:

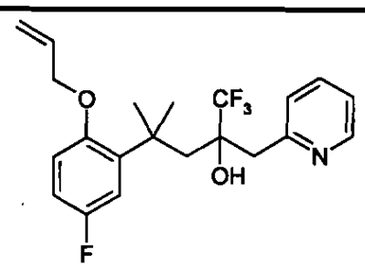
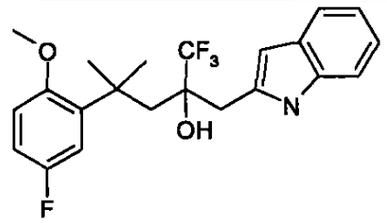
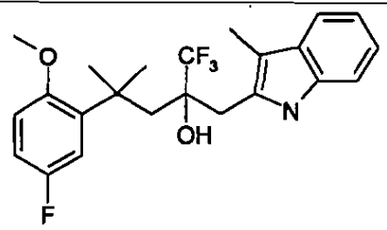
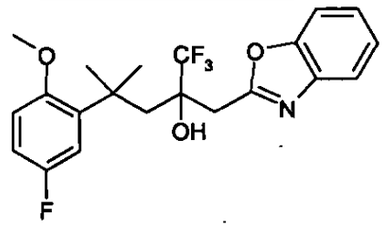
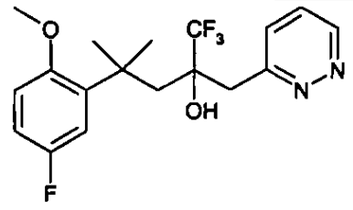
Compound Name	Compound Structure
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(4,6-dimethylpyridin-2-ylmethyl)-4-methylpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(pyridin-2-ylmethyl)-4-methylpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(6-methylpyridin-2-ylmethyl)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(4-methylpyridin-2-ylmethyl)pentan-2-ol	
4-Fluoro-2-(4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-pyridin-2-ylmethylbutyl)phenol	

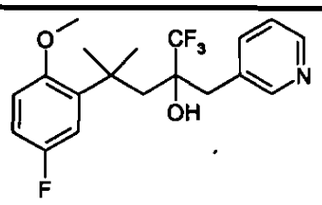
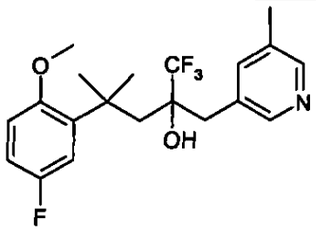
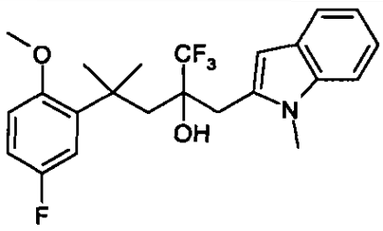
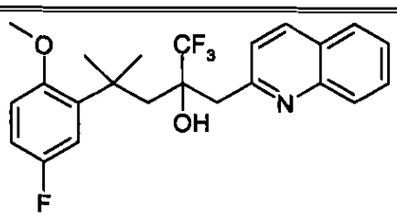
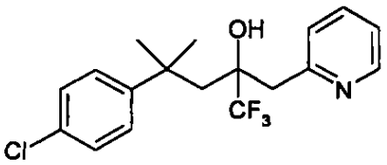
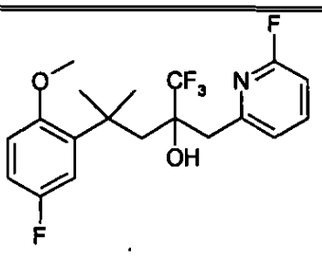
2-(4,5-Dimethylthiazol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol	
2-(4,5-Dimethyloxazol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(3-methylpyridin-2-ylmethyl)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(5-methylpyridin-2-ylmethyl)pentan-2-ol	
2-Benzothiazol-2-ylmethyl-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol	

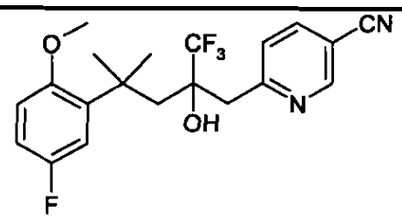
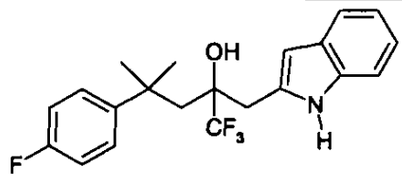
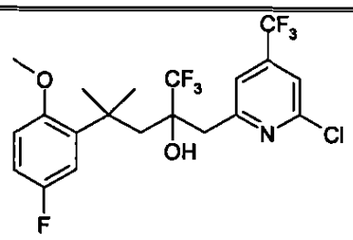
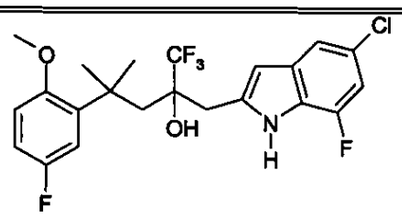
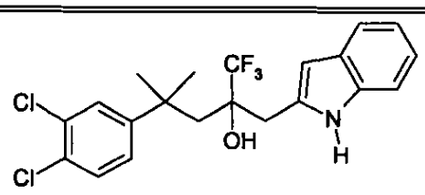
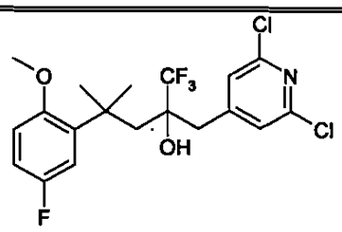
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(5-phenylbenzoxazol-2-ylmethyl)pentan-2-ol	
2-Benzofuran-2-ylmethyl-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(3-methylbenzofuran-2-ylmethyl)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-thiophen-2-ylmethylpentan-2-ol	
5-(5-Fluoro-2-methoxyphenyl)-5-methyl-2-pyridin-2-yl-3-trifluoromethylhexan-3-ol	
5-(5-Fluoro-2-methoxyphenyl)-5-methyl-2-pyridin-2-yl-3-trifluoromethylhexan-3-ol	

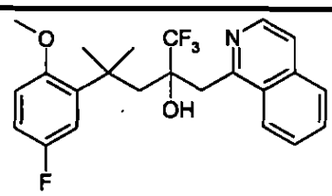
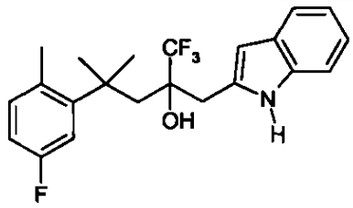
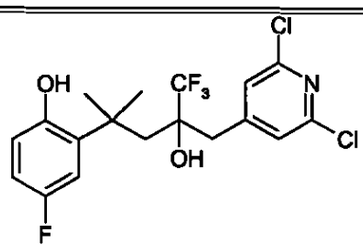
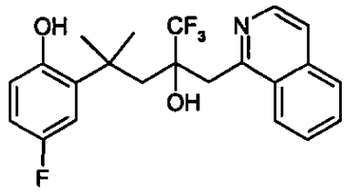
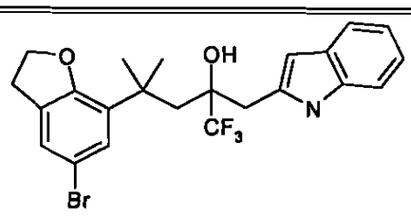
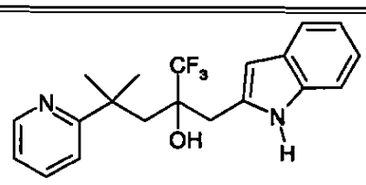
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(5-methylbenzooxazol-2-ylmethyl)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(5-methylbenzothiazol-2-ylmethyl)pentan-2-ol	
4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(5-methylbenzooxazol-2-ylmethyl)butyl]phenol	
4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(5-methylbenzothiazol-2-ylmethyl)butyl]phenol	
1,1,1-Trifluoro-4-methyl-4-phenyl-2-pyridin-2-ylmethylpentan-2-ol	
2-(4,6-Dimethylpyridin-2-ylmethyl)-1,1,1-trifluoro-4-methyl-4-phenylpentan-2-ol	

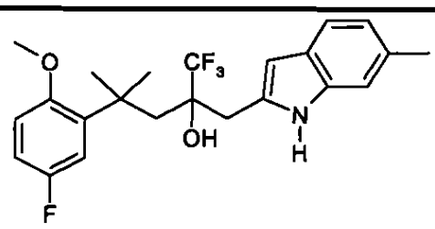
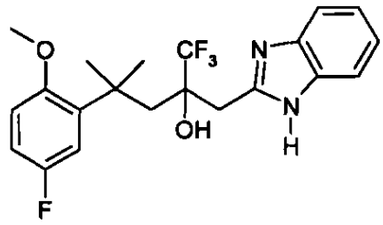
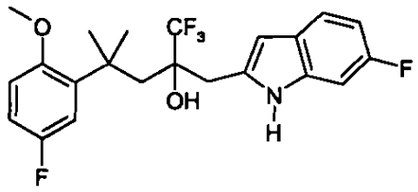
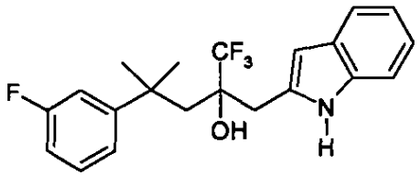
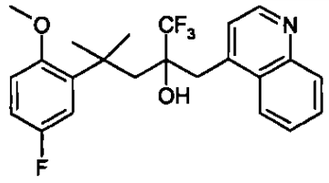
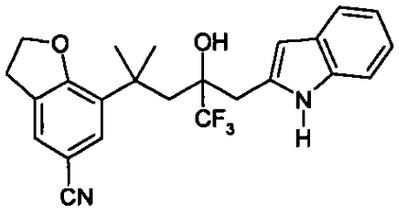
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1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(4-methylquinolin-2-ylmethyl)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1-phenyl-1*H*-pyrazol-3-ylmethyl)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1-methyl-1*H*-imidazol-2-ylmethyl)pentan-2-ol	
5-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-3-phenylisoxazole-4-carboxylic acid methylamide	
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-pyrazin-2-ylmethylpentan-2-ol	

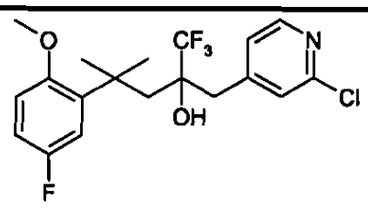
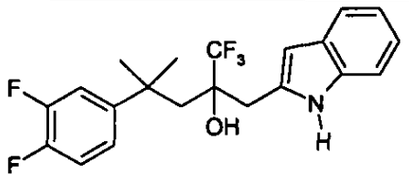
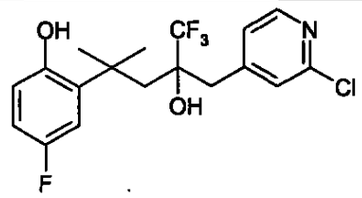
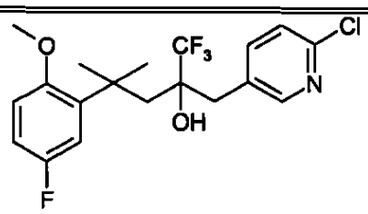
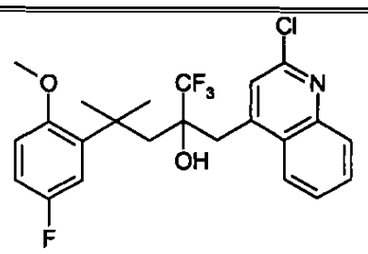
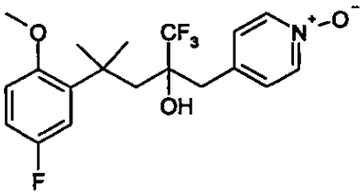
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1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(3-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol	
2-Benzooxazol-2-ylmethyl-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-pyridazin-3-ylmethylpentan-2-ol	

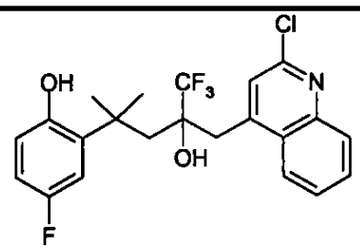
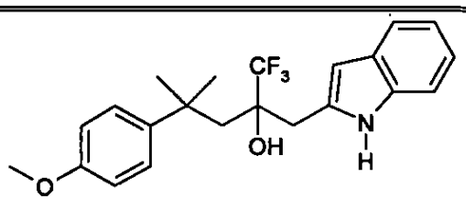
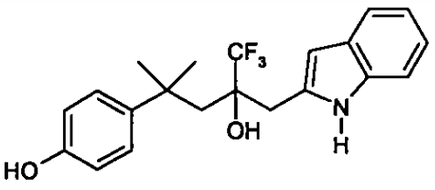
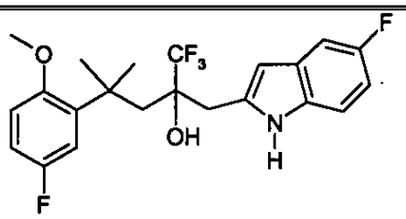
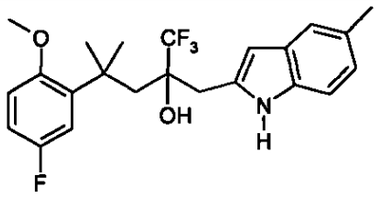
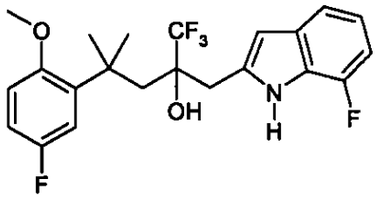
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-pyridin-3-ylmethylpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(5-methylpyridin-3-ylmethyl)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-quinolin-2-ylmethylpentan-2-ol	
4-(4-Chlorophenyl)-1,1,1-trifluoro-4-methyl-2-pyridin-2-ylmethylpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(6-fluoropyridin-2-ylmethyl)-4-methylpentan-2-ol	

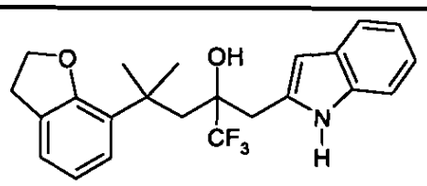
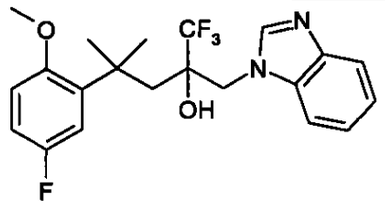
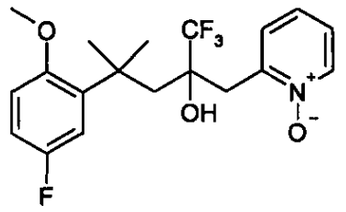
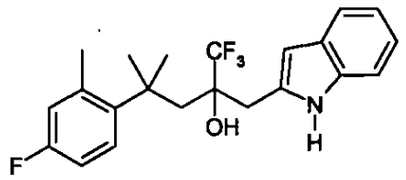
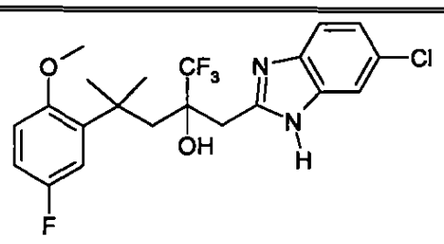
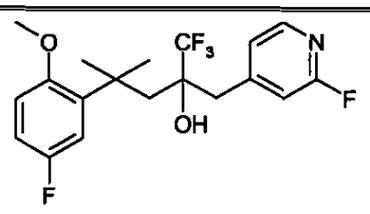
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2-(6-Chloro-4-trifluoromethylpyridin-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol	
2-(5-Chloro-7-fluoro-1*H*-indol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol	
4-(3,4-Dichlorophenyl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol	
2-(2,6-Dichloropyridin-4-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol	

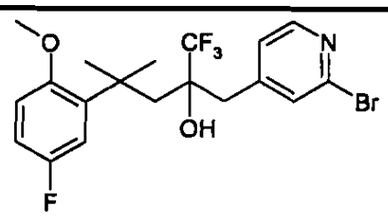
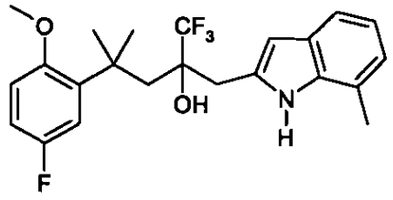
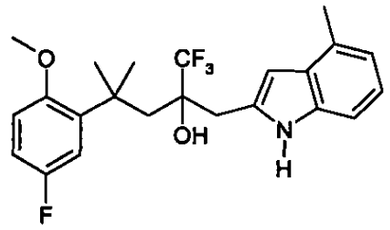
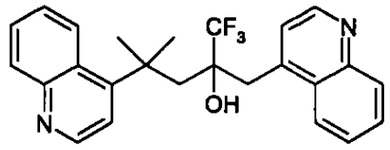
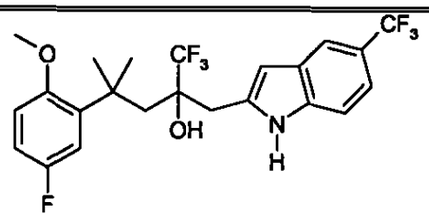
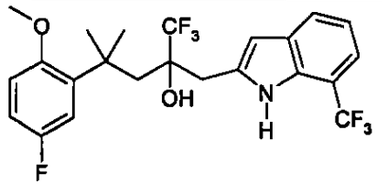
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-isoquinolin-1-ylmethyl-4-methylpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol	
2-[3-(2,6-Dichloropyridin-4-ylmethyl)-4,4,4-trifluoro-3-hydroxy-1,1-dimethylbutyl]-4-fluorophenol	
4-Fluoro-2-(4,4,4-trifluoro-3-hydroxy-3-isoquinolin-1-ylmethyl-1,1-dimethylbutyl)phenol	
4-(5-Bromo-2,3-dihydrobenzofuran-7-yl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol	
1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-pyridin-2-ylpentan-2-ol	

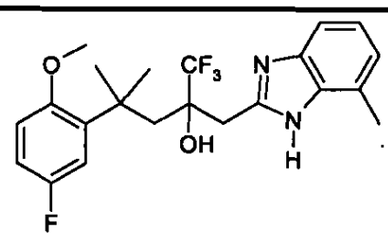
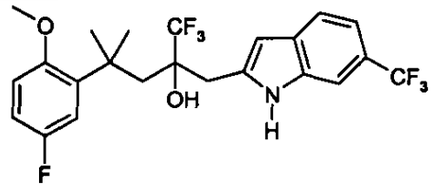
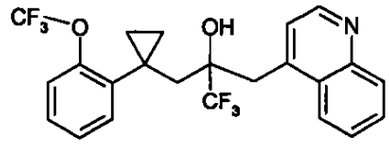
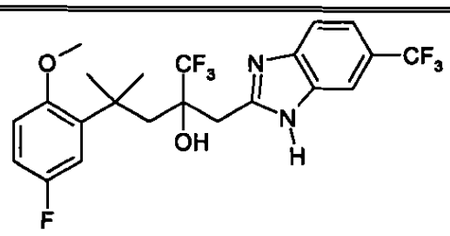
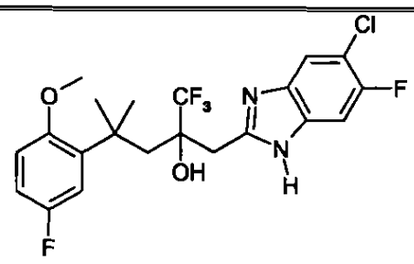
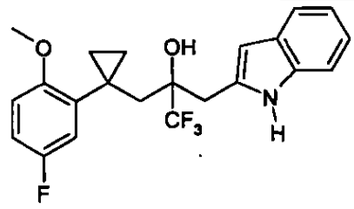
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2-(1*H*-Benzimidazol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol	
1,1,1-Trifluoro-2-(6-fluoro-1*H*-indol-2-ylmethyl)-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol	
1,1,1-Trifluoro-4-(3-fluorophenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(quinolin-4-ylmethyl)pentan-2-ol	
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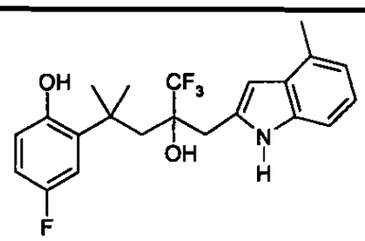
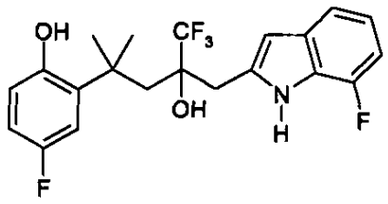
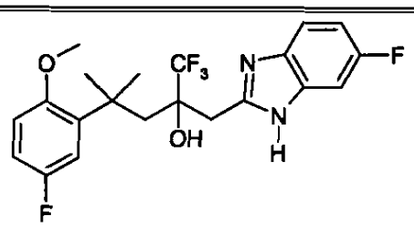
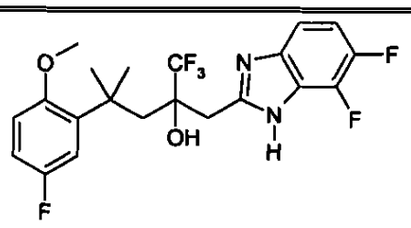
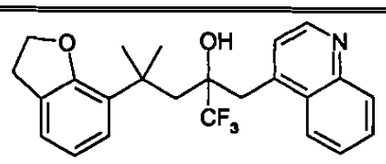
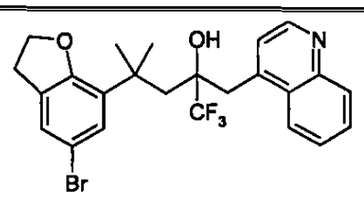
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(2-chloropyridin-4-ylmethyl)pentan-2-ol	
4-(3,4-Difluorophenyl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-hydroxyphenyl)-4-methyl-2-(2-chloropyridin-4-ylmethyl)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(2-chloropyridin-5-ylmethyl)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(2-chloroquinolin-4-ylmethyl)pentan-2-ol	
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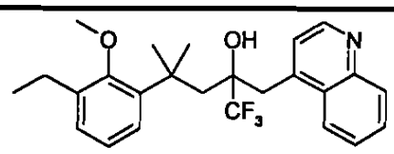
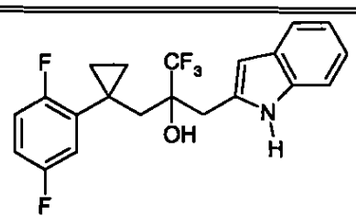
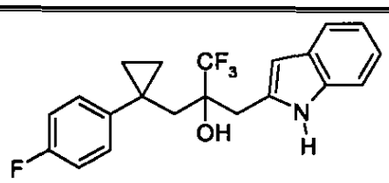
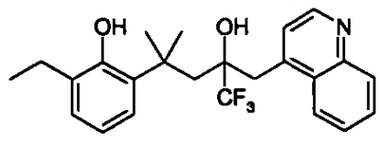
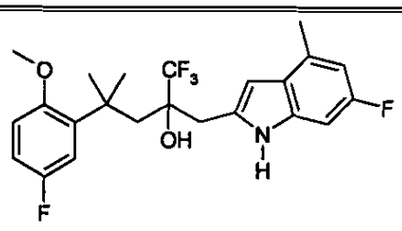
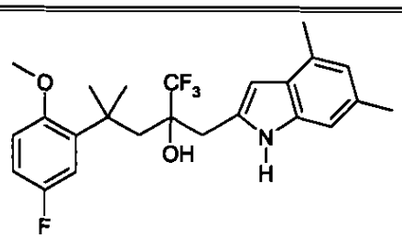
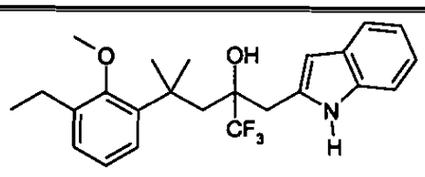
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1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-(4-methoxyphenyl)-4-methylpentan-2-ol	
4-[4,4,4-Trifluoro-3-hydroxy-3-(1*H*-indol-2-ylmethyl)-1,1-dimethylbutyl]phenol	
1,1,1-Trifluoro-2-(5-fluoro-1*H*-indol-2-ylmethyl)-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol	
1,1,1-Trifluoro-2-(5-methyl-1*H*-indol-2-ylmethyl)-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol	
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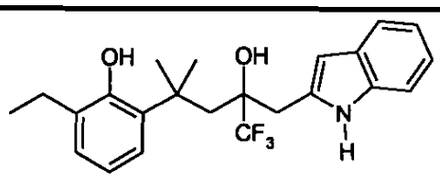
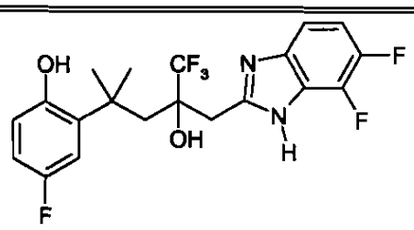
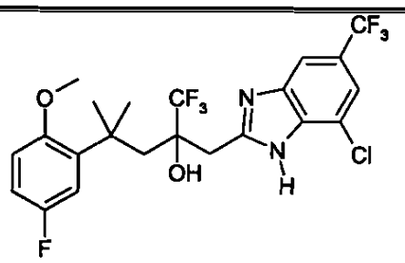
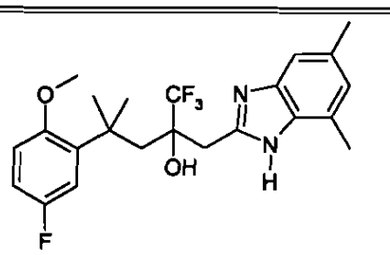
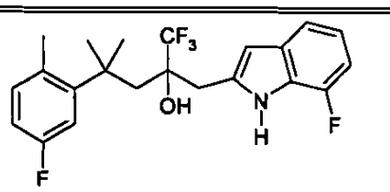
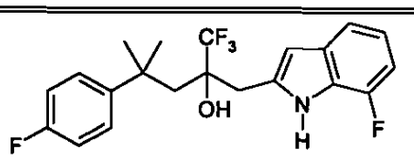
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2-Benzimidazol-1-ylmethyl-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1-oxypyridin-2-ylmethyl)pentan-2-ol	
1,1,1-Trifluoro-4-(4-fluoro-2-methylphenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(6-chlorobenzimidazol-2-ylmethyl)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(2-fluoropyridin-4-ylmethyl)pentan-2-ol	

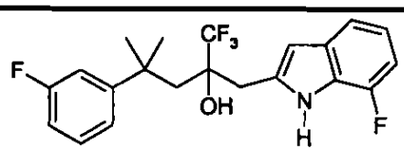
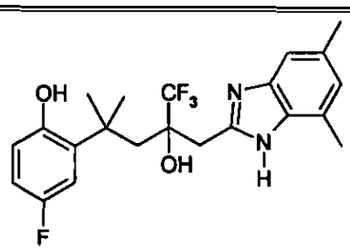
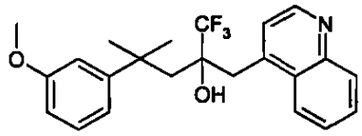
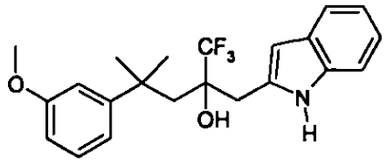
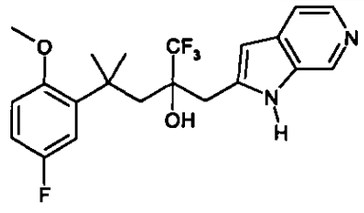
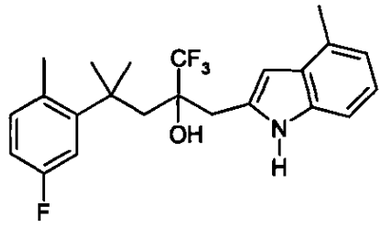
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1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(7-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(4-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol	
1,1,1-Trifluoro-4-methyl-4-quinolin-4-yl-2-quinolin-4-ylmethylpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(7-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol	

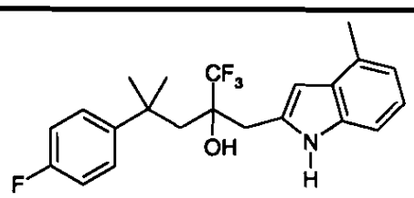
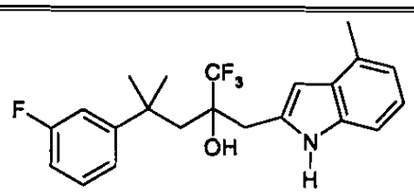
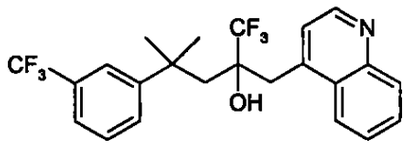
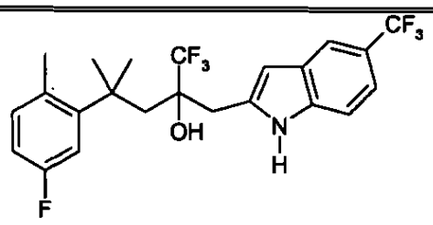
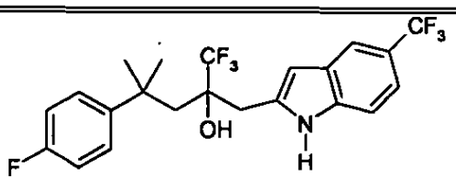
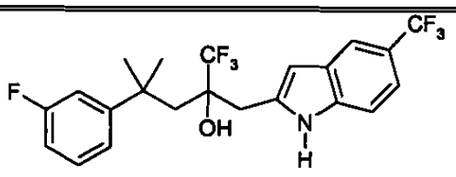
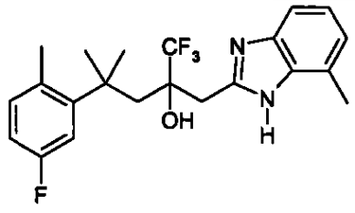
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(7-methyl-1*H*-benzoimidazol-2-ylmethyl)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(6-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol	
1,1,1-Trifluoro-2-quinolin-4-ylmethyl-3-[1-(2-trifluoromethoxyphenyl)cyclopropyl]propan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(6-trifluoromethyl-1*H*-benzoimidazol-2-ylmethyl)pentan-2-ol	
2-(5-Chloro-6-fluoro-1*H*-benzoimidazol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol	
1,1,1-Trifluoro-3-[1-(5-fluoro-2-methoxyphenyl)cyclopropyl]-2-(1*H*-indol-2-ylmethyl)propan-2-ol	

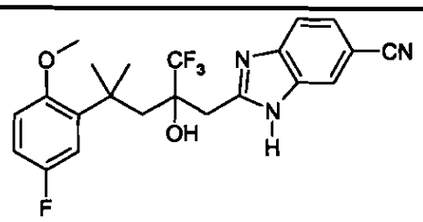
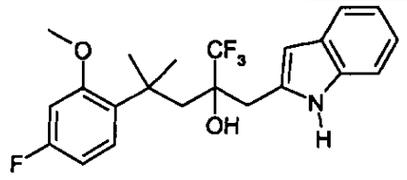
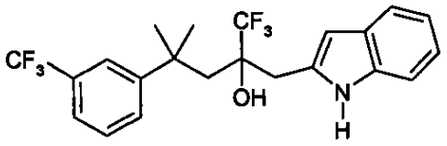
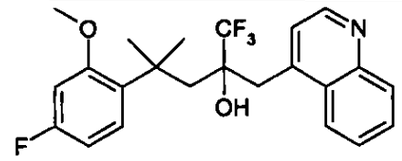
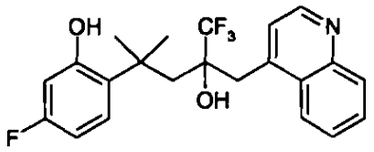
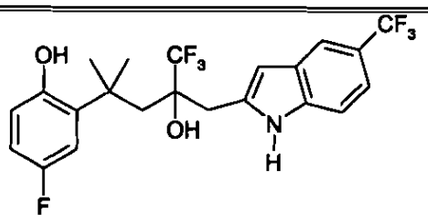
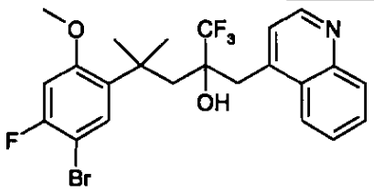
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4-Fluoro-2-[4,4,4-trifluoro-3-(7-fluoro-1*H*-indol-2-ylmethyl)-3-hydroxy-1,1-dimethylbutyl]phenol	
1,1,1-Trifluoro-2-(6-fluoro-1*H*-benzoimidazol-2-ylmethyl)-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol	
2-(6,7-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol	
4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol	
4-(5-Bromo-2,3-dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol	

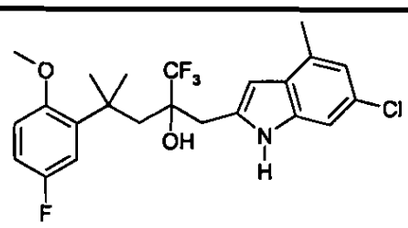
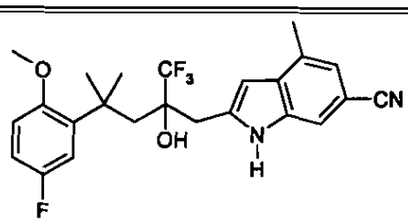
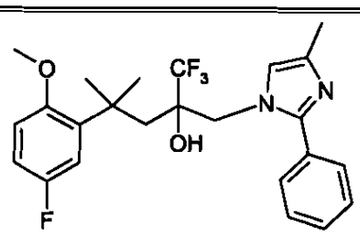
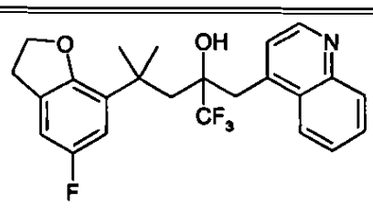
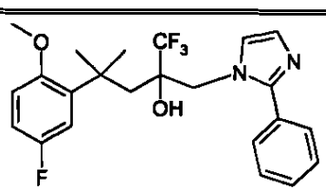
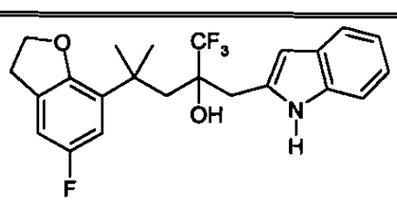
4-(3-Ethyl-2-methoxyphenyl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol	
3-[1-(2,5-Difluorophenyl)cyclopropyl]-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)propan-2-ol	
1,1,1-Trifluoro-3-[1-(4-fluorophenyl)cyclopropyl]-2-(1*H*-indol-2-ylmethyl)propan-2-ol	
2-Ethyl-6-(4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol	
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(6-fluoro-4-methyl-1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol	
2-(4,6-Dimethyl-1*H*-indol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol	
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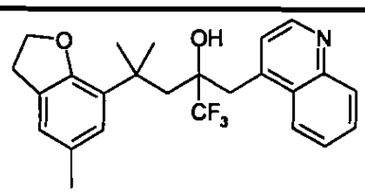
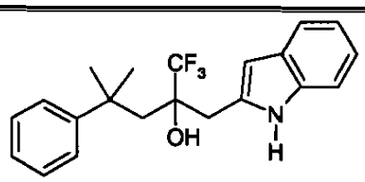
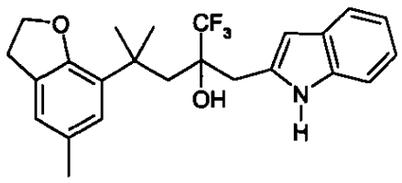
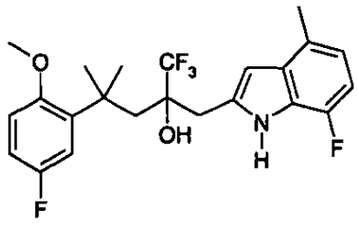
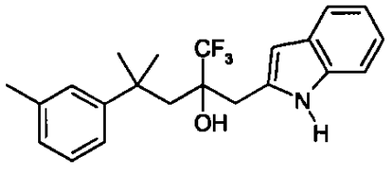
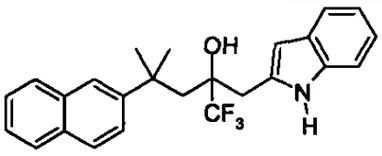
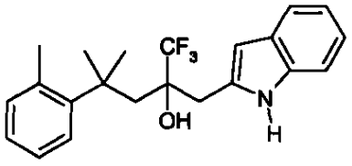
2-Ethyl-6-[4,4,4-trifluoro-3-hydroxy-3-(1*H*-indol-2-ylmethyl)-1,1-dimethylbutyl]phenol	
2-[3-(6,7-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-4,4,4-trifluoro-3-hydroxy-1,1-dimethylbutyl]-4-fluorophenol	
2-(7-Chloro-5-trifluoromethyl-1*H*-benzoimidazol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol	
2-(5,7-Dimethyl-1*H*-benzoimidazol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol	
1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-(5-fluoro-2-methylphenyl)-4-methylpentan-2-ol	
1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-(4-fluorophenyl)-4-methylpentan-2-ol	

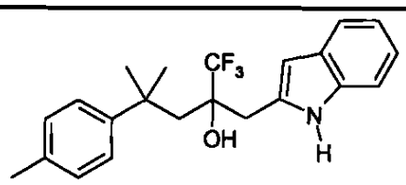
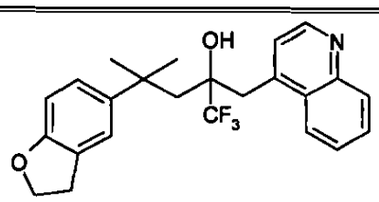
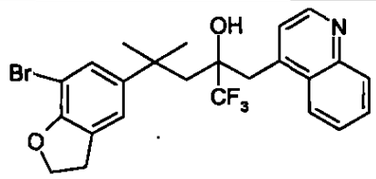
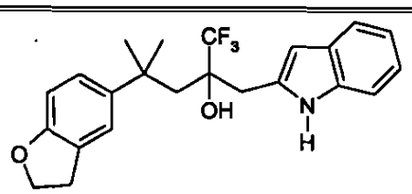
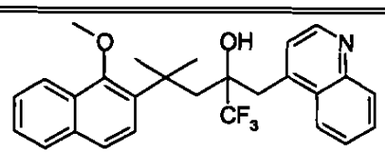
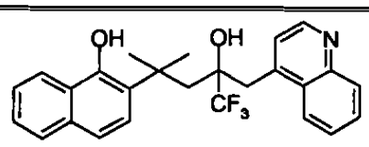
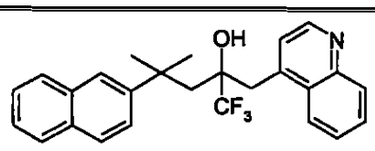
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2-[3-(5,7-Dimethyl-1*H*-benzoimidazol-2-ylmethyl)-4,4,4-trifluoro-3-hydroxy-1,1-dimethylbutyl]-4-fluorophenol	
1,1,1-Trifluoro-4-(3-methoxyphenyl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol	
1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-(3-methoxyphenyl)-4-methylpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-4-methyl-2-(4-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol	

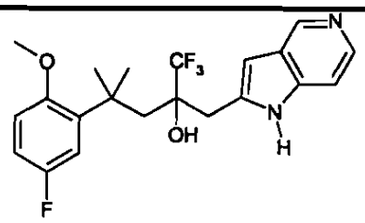
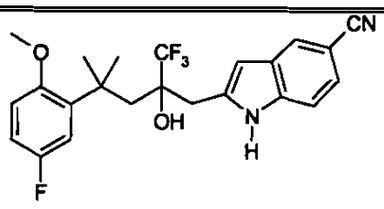
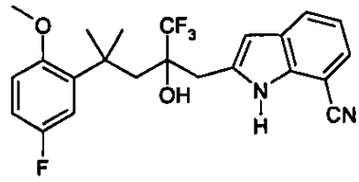
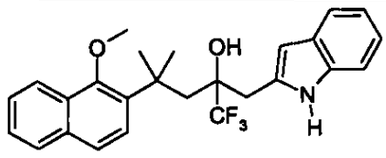
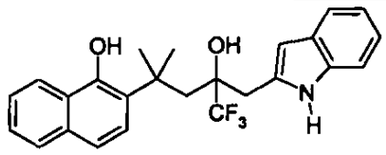
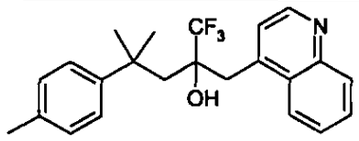
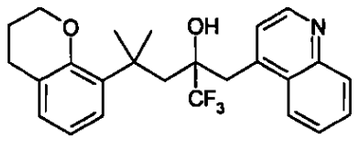
1,1,1-Trifluoro-4-(4-fluorophenyl)-4-methyl-2-(4-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol	
1,1,1-Trifluoro-4-(3-fluorophenyl)-4-methyl-2-(4-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol	
1,1,1-Trifluoro-4-methyl-2-quinolin-4-ylmethyl-4-(3-trifluoromethylphenyl)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-4-methyl-2-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol	
1,1,1-Trifluoro-4-(4-fluorophenyl)-4-methyl-2-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol	
1,1,1-Trifluoro-4-(3-fluorophenyl)-4-methyl-2-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-4-methyl-2-(7-methyl-1*H*-benzoimidazol-2-ylmethyl)pentan-2-ol	

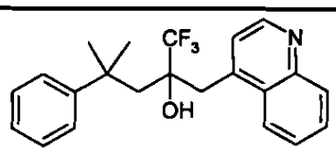
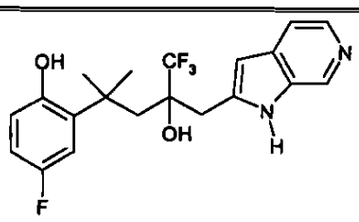
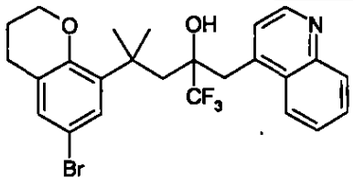
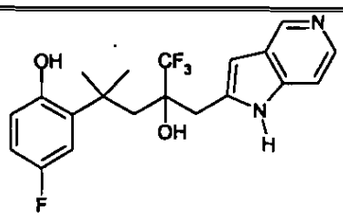
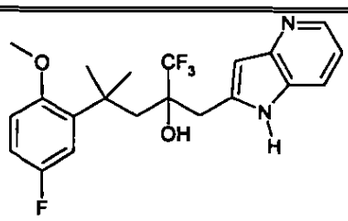
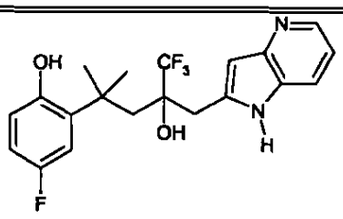
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1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol	
1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-(3-trifluoromethylphenyl)pentan-2-ol	
1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol	
5-Fluoro-2-(4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol	
4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)butyl]phenol	
4-(5-Bromo-4-fluoro-2-methoxyphenyl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol	

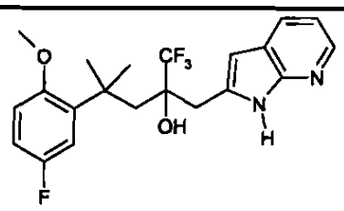
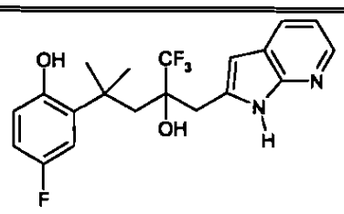
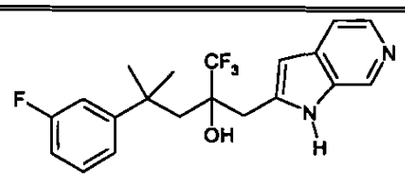
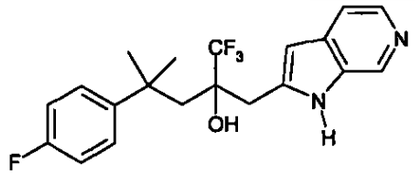
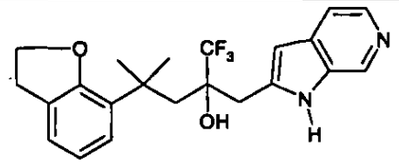
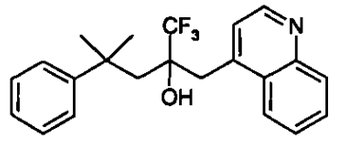
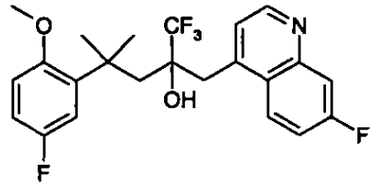
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2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile	
2-(2-Phenyl-4-methylimidazol-1-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2,3-dihydrobenzofuran-7-yl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol	
2-(2-Phenylimidazol-1-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2,3-dihydrobenzofuran-7-yl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol	

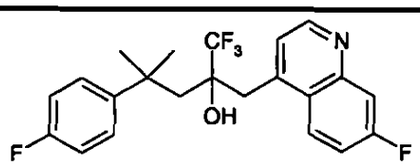
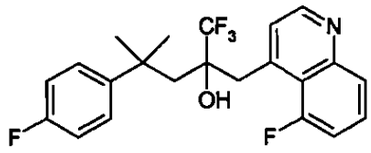
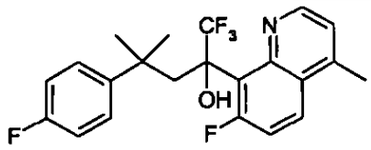
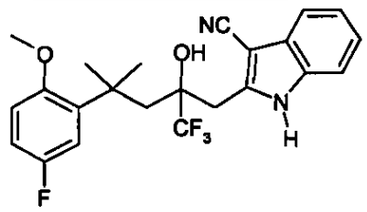
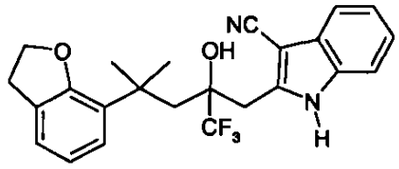
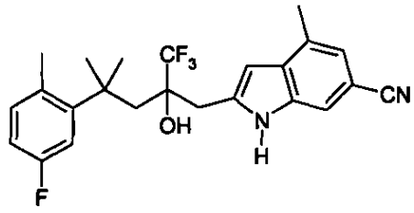
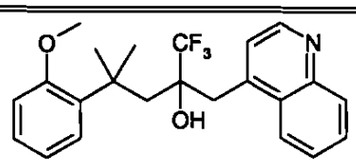
1,1,1-Trifluoro-4-methyl-4-(5-methyl-2,3-dihydrobenzofuran-7-yl)-2-quinolin-4-ylmethylpentan-2-ol	
1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-phenylpentan-2-ol	
1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-(5-methyl-2,3-dihydrobenzofuran-7-yl)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(7-fluoro-4-methyl-1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol	
1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-*m*-tolylpentan-2-ol	
1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-naphthalen-2-ylpentan-2-ol	
1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-*o*-tolylpentan-2-ol	

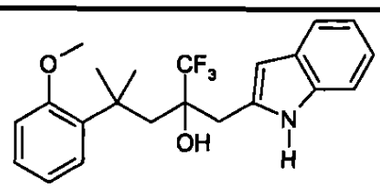
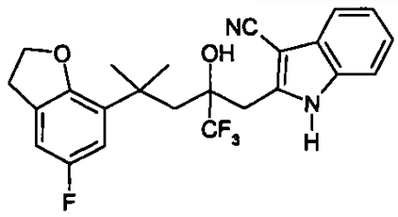
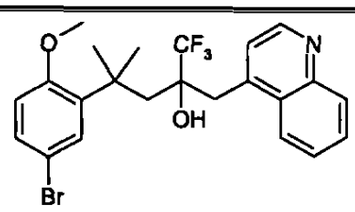
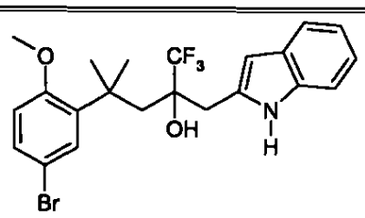
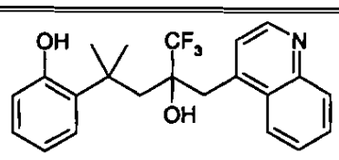
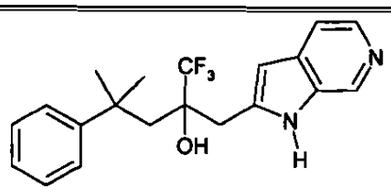
1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-*p*-tolylpentan-2-ol	
4-(2,3-Dihydrobenzofuran-5-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol	
4-(7-Bromo-2,3-dihydrobenzofuran-5-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol	
4-(2,3-Dihydrobenzofuran-5-yl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol	
1,1,1-Trifluoro-4-(1-methoxynaphthalen-2-yl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol	
2-(4,4,4-Trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)naphthalen-1-ol	
1,1,1-Trifluoro-4-methyl-4-naphthalen-2-yl-2-quinolin-4-ylmethylpentan-2-ol	

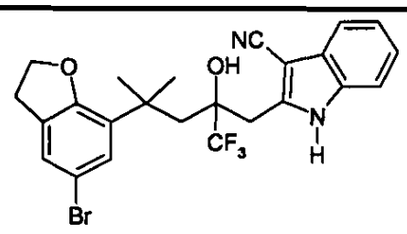
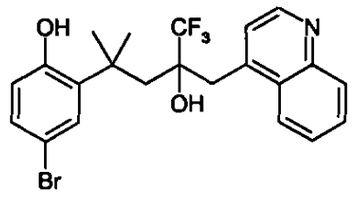
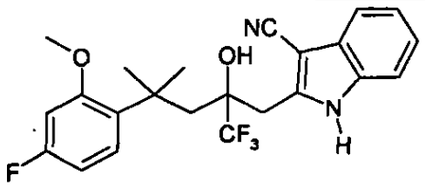
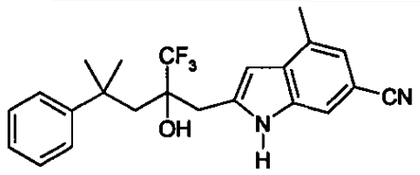
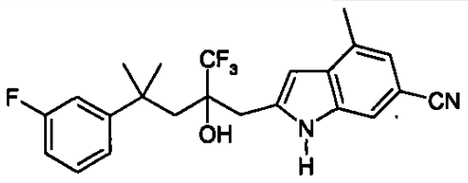
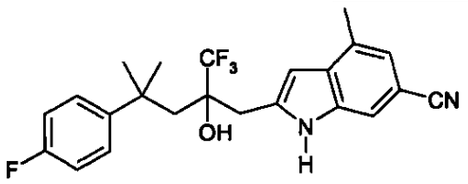
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol	
2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile	
2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-7-carbonitrile	
1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-(1-methoxynaphthalen-2-yl)-4-methylpentan-2-ol	
2-[4,4,4-Trifluoro-3-hydroxy-3-(1*H*-indol-2-ylmethyl)-1,1-dimethylbutyl]naphthalen-1-ol	
1,1,1-Trifluoro-4-methyl-2-quinolin-4-ylmethyl-4-*p*-tolylpentan-2-ol	
4-Chroman-8-yl-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol	

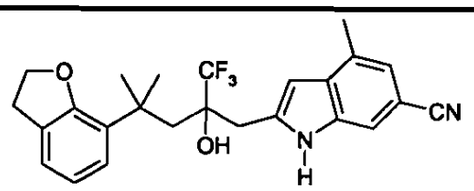
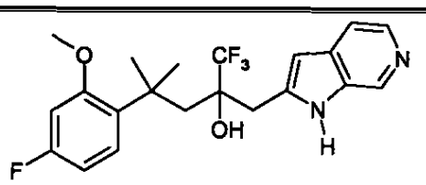
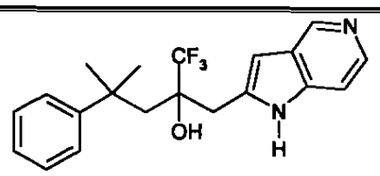
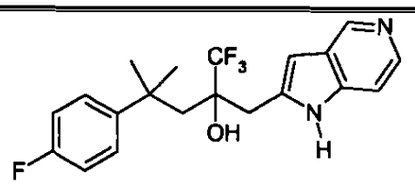
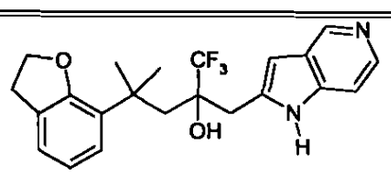
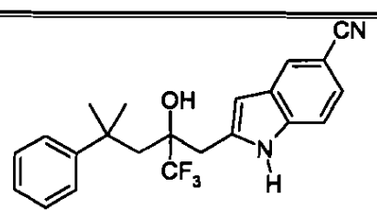
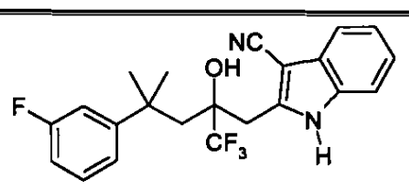
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4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)butyl]phenol	
4-(6-Bromochroman-8-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol	
4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)butyl]phenol	
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*b*]pyridin-2-ylmethyl)pentan-2-ol	
4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[3,2-*b*]pyridin-2-ylmethyl)butyl]phenol	

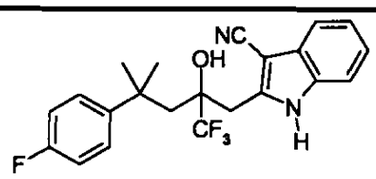
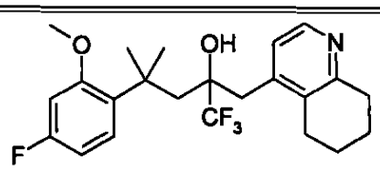
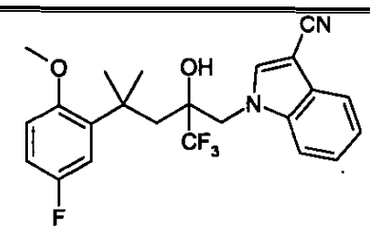
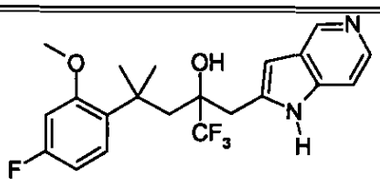
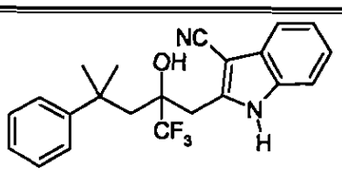
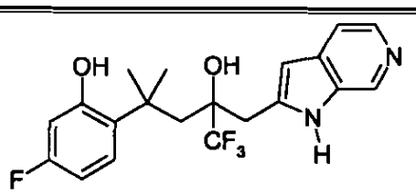
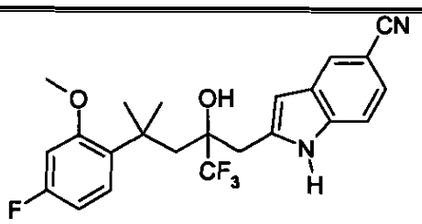
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*b*]pyridin-2-ylmethyl)pentan-2-ol	
4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[2,3-*b*]pyridin-2-ylmethyl)butyl]phenol	
1,1,1-Trifluoro-4-(3-fluorophenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol	
1,1,1-Trifluoro-4-(4-fluorophenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol	
4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol	
1,1,1-Trifluoro-4-methyl-4-phenyl-2-quinolin-4-ylmethylpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(7-fluoroquinolin-4-ylmethyl)-4-methylpentan-2-ol	

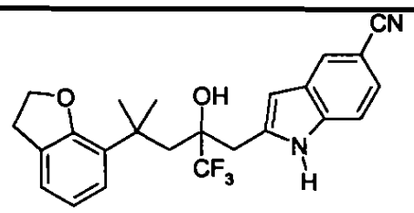
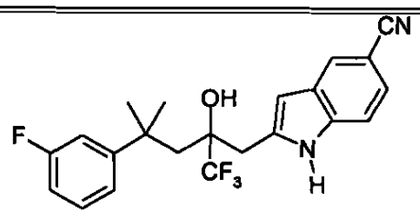
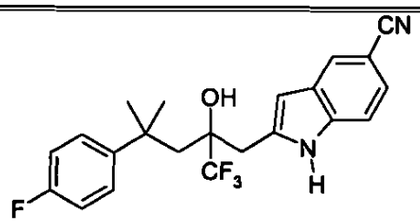
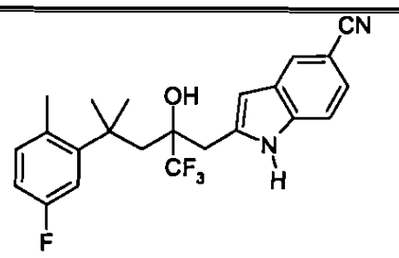
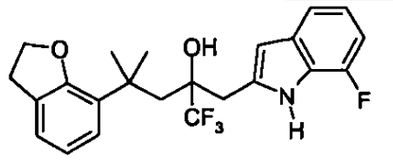
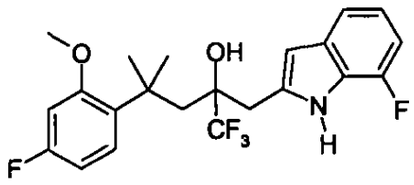
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1,1,1-Trifluoro-4-(4-fluorophenyl)-2-(5-fluoroquinolin-4-ylmethyl)-4-methylpentan-2-ol	
1,1,1-Trifluoro-2-(7-fluoro-4-methylquinolin-8-yl)-4-(4-fluorophenyl)-4-methylpentan-2-ol	
2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile	
2-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile	
2-[4-(5-Fluoro-2-methylphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile	
1,1,1-Trifluoro-4-(2-methoxyphenyl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol	

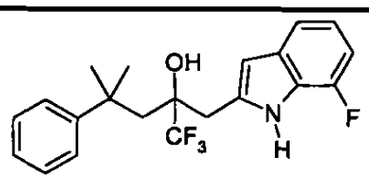
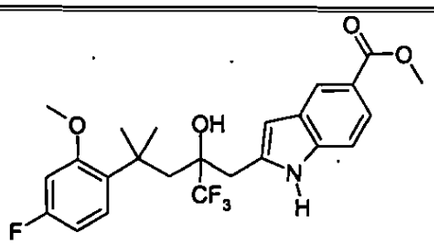
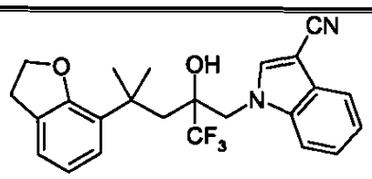
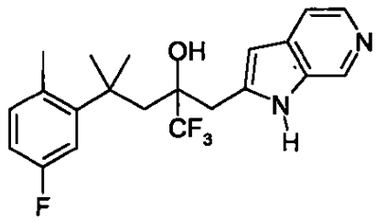
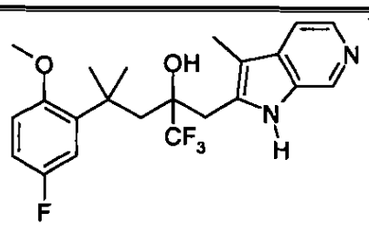
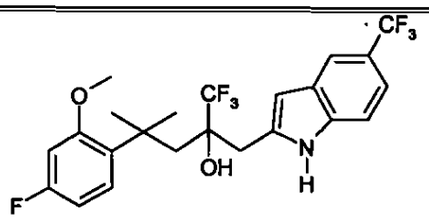
1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-(2-methoxyphenyl)-4-methylpentan-2-ol	
2-[4-(5-Fluoro-2,3-dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile	
4-(5-Bromo-2-methoxyphenyl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol	
4-(5-Bromo-2-methoxyphenyl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol	
2-(4,4,4-Trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol	
1,1,1-Trifluoro-4-methyl-4-phenyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol	

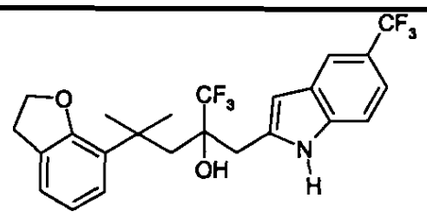
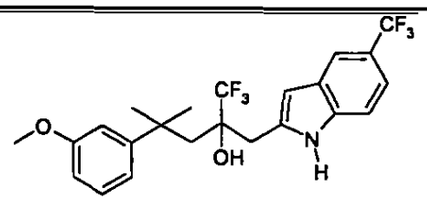
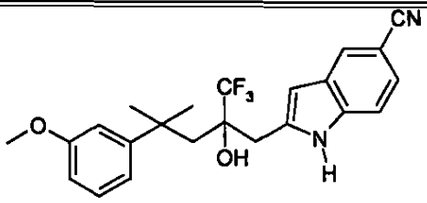
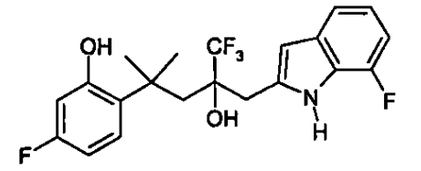
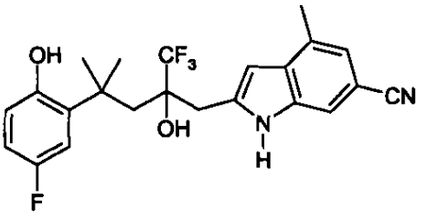
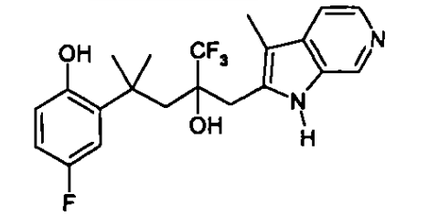
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4-Bromo-2-(4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol	
2-[4-(4-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile	
2-(2-Hydroxy-4-methyl-4-phenyl-2-trifluoromethylpentyl)-4-methyl-1*H*-indole-6-carbonitrile	
2-[4-(3-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile	
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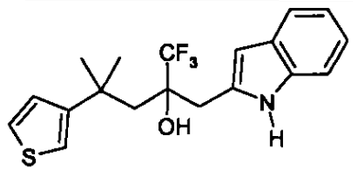
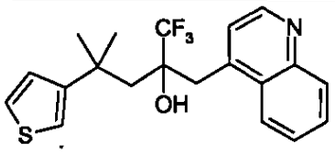
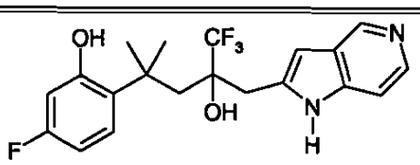
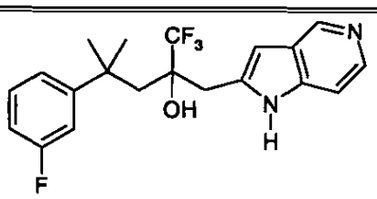
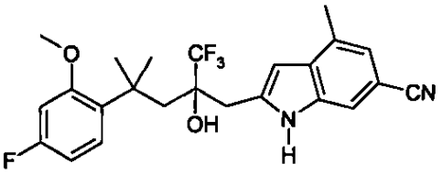
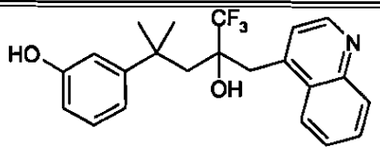
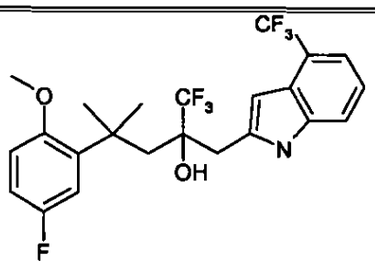
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1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol	
1,1,1-Trifluoro-4-methyl-4-phenyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol	
1,1,1-Trifluoro-4-(4-fluorophenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol	
4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol	
2-(2-Hydroxy-4-methyl-4-phenyl-2-trifluoromethylpentyl)-1*H*-indole-5-carbonitrile	
2-[4-(3-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile	

2-[4-(4-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile	
1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-(5,6,7,8-tetrahydroquinolin-4-ylmethyl)pentan-2-ol	
1-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile	
1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol	
2-(2-Hydroxy-4-methyl-4-phenyl-2-trifluoromethylpentyl)-1*H*-indole-3-carbonitrile	
5-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)butyl]phenol	
2-[4-(4-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile	

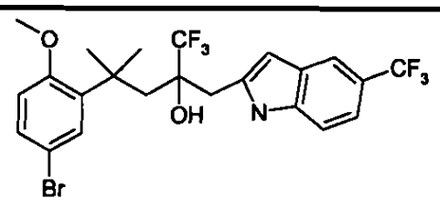
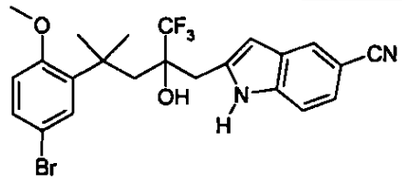
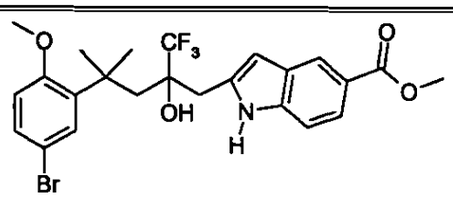
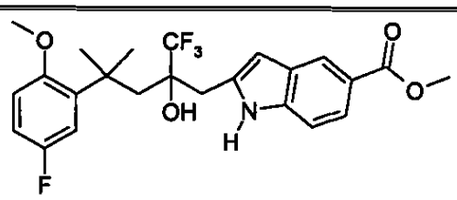
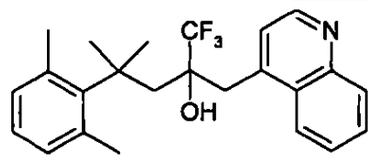
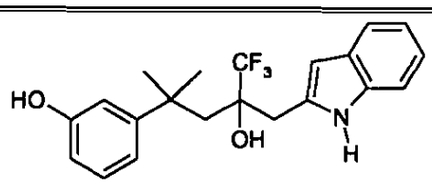
2-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile	
2-[4-(3-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile	
2-[4-(4-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile	
2-[4-(5-Fluoro-2-methylphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile	
4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)4-methylpentan-2-ol	
1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-(4-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol	

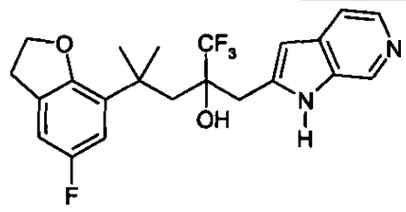
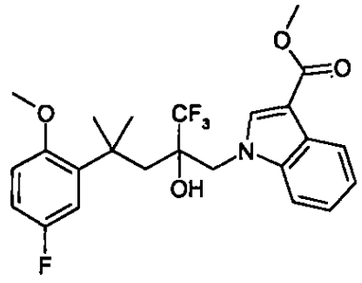
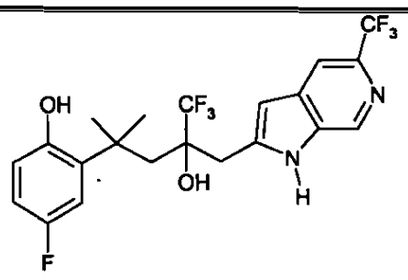
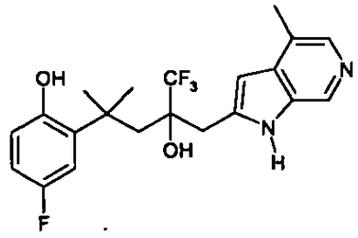
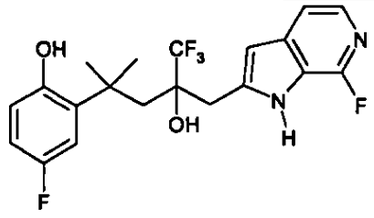
1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-methyl-4-phenylpentan-2-ol	
2-[4-(4-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carboxylic acid methyl ester	
1-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile	
1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(3-methyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol	
1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol	

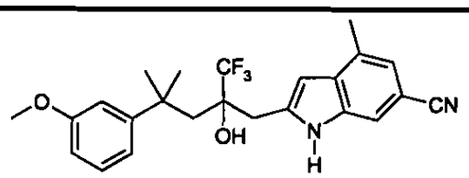
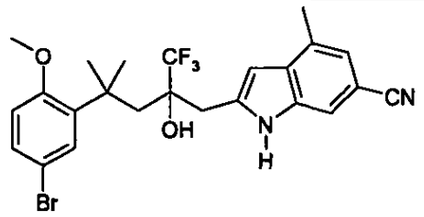
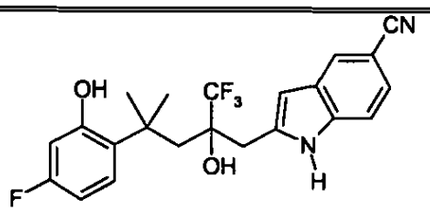
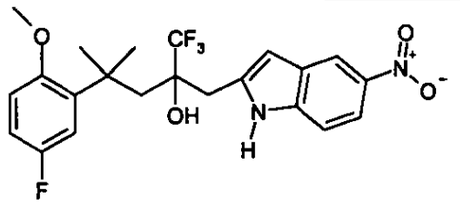
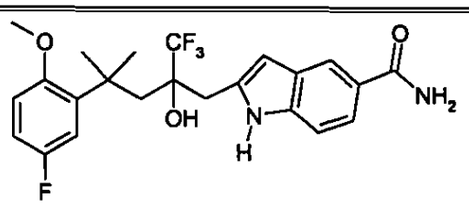
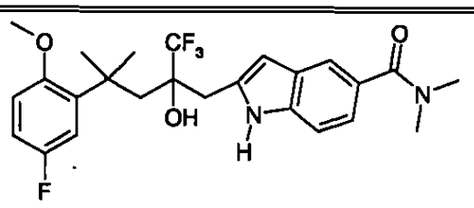
4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol	
1,1,1-Trifluoro-4-(3-methoxyphenyl)-4-methyl-2-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol	
2-[2-Hydroxy-4-(3-methoxyphenyl)-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile	
5-Fluoro-2-[4,4,4-trifluoro-3-(7-fluoro-1*H*-indol-2-ylmethyl)-3-hydroxy-1,1-dimethylbutyl]phenol	
2-[4-(5-Fluoro-2-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile	
4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(3-methyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)butyl]phenol	

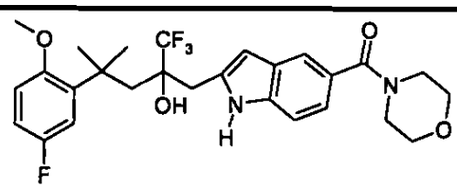
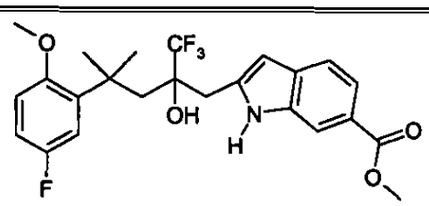
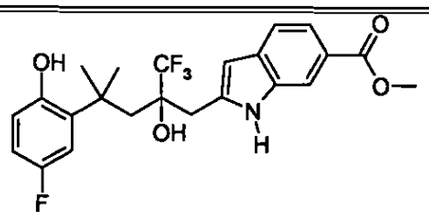
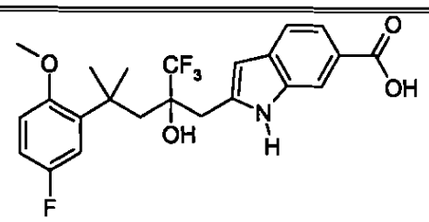
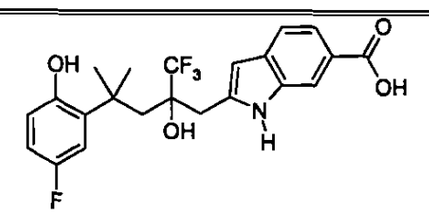
1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-thiophen-3-ylpentan-2-ol	
1,1,1-Trifluoro-4-methyl-2-quinolin-4-ylmethyl-4-thiophen-3-ylpentan-2-ol	
5-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)butyl]phenol	
1,1,1-Trifluoro-4-(3-fluorophenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol	
2-[4-(4-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile	
3-(4,4,4-Trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol	
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(4-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol	

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4-(5-Bromo-2-methoxyphenyl)-1,1,1-trifluoro-4-methyl-2-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol	
2-[4-(5-Bromo-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile	
2-[4-(5-Bromo-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carboxylic acid methyl ester	
2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carboxylic acid methyl ester	
4-(2,6-Dimethylphenyl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol	
3-[4,4,4-Trifluoro-3-hydroxy-3-(1*H*-indol-2-ylmethyl)-1,1-dimethylbutyl]phenol	

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihydrobenzofuran-7-yl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol	
1-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carboxylic acid methyl ester	
4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[2,3-*c*]-[2-trifluoromethylpyridin]-2-ylmethyl)butyl]phenol	
4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[2,3-*c*]-[3-methylpyridin]-2-ylmethyl)butyl]phenol	
4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[2,3-*c*]-[2-fluoropyridin]-2-ylmethyl)butyl]phenol	

2-[2-Hydroxy-4-(3-methoxyphenyl)-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile	
2-[4-(5-Bromo-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile	
2-[4-(4-Fluoro-2-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile	
1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(5-nitro-1*H*-indol-2-ylmethyl)pentan-2-ol	
2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carboxylic acid amide	
2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carboxylic acid dimethylamide	

{2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indol-5-yl}morpholin-4-ylmethanone	
2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-6-carboxylic acid methyl ester	
2-[4-(5-Fluoro-2-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-6-carboxylic acid methyl ester	
2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-6-carboxylic acid	
2-[4-(5-Fluoro-2-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-6-carboxylic acid	
or a tautomer, prodrug, solvate, or salt thereof.	

Preferred compounds of Formula (IA) include the following:

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(pyridin-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(5-phenylbenzoxazol-2-ylmethyl)pentan-2-ol;

2-Benzofuran-2-ylmethyl-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(3-methylbenzofuran-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(3-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

6-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]nicotinonitrile;

2-(1*H*-Indol-2-ylmethyl)-1,1,1-trifluoro-4-(4-fluorophenyl)-4-methylpentan-2-ol;

2-(6-Chloro-4-trifluoromethylpyridin-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

2-(5-Chloro-7-fluoro-1*H*-indol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

4-(3,4-Dichlorophenyl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-(2,6-Dichloropyridin-4-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-[3-(2,6-Dichloropyridin-4-ylmethyl)-4,4,4-trifluoro-3-hydroxy-1,1-dimethylbutyl]-4-fluorophenol;

4-Fluoro-2-(4,4,4-trifluoro-3-hydroxy-3-isoquinolin-1-ylmethyl-1,1-dimethylbutyl)phenol;

4-(5-Bromo-2,3-dihydrobenzofuran-7-yl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-pyridin-2-ylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(6-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

2-(1*H*-Benzimidazol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(6-fluoro-1*H*-indol-2-ylmethyl)-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorophenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(quinolin-4-ylmethyl)pentan-2-ol;

4-(2,3-dihydro-5-cyanobenzofuran-7-yl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(2-chloropyridin-4-ylmethyl)pentan-2-ol;

4-(3,4-Difluorophenyl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-hydroxyphenyl)-4-methyl-2-(2-chloropyridin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(2-chloroquinolin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-hydroxyphenyl)-4-methyl-2-(2-chloroquinolin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-(4-methoxyphenyl)-4-methylpentan-2-ol;

4-[4,4,4-Trifluoro-3-hydroxy-3-(1*H*-indol-2-ylmethyl)-1,1-dimethylbutyl]phenol;

1,1,1-Trifluoro-2-(5-fluoro-1*H*-indol-2-ylmethyl)-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(5-methyl-1*H*-indol-2-ylmethyl)-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

4-(2,3-dihydrobenzofuran-7-yl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-Benzimidazol-1-ylmethyl-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-methylphenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(6-chlorobenzimidazol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(2-fluoropyridin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(2-bromopyridin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(7-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(4-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(7-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(7-methyl-1*H*-benzoimidazol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(6-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(6-trifluoromethyl-1*H*-benzoimidazol-2-ylmethyl)pentan-2-ol;

2-(5-Chloro-6-fluoro-1*H*-benzoimidazol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-3-[1-(5-fluoro-2-methoxyphenyl)cyclopropyl]-2-(1*H*-indol-2-ylmethyl)propan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(4-methyl-1*H*-indol-2-ylmethyl)butyl]phenol;

4-Fluoro-2-[4,4,4-trifluoro-3-(7-fluoro-1*H*-indol-2-ylmethyl)-3-hydroxy-1,1-dimethylbutyl]phenol;

1,1,1-Trifluoro-2-(6-fluoro-1*H*-benzoimidazol-2-ylmethyl)-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

2-(6,7-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(5-Bromo-2,3-dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(3-Ethyl-2-methoxyphenyl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-3-[1-(4-fluorophenyl)cyclopropyl]-2-(1*H*-indol-2-ylmethyl)propan-2-ol;

2-Ethyl-6-(4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(6-fluoro-4-methyl-1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-(4,6-Dimethyl-1*H*-indol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

4-(3-Ethyl-2-methoxyphenyl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-Ethyl-6-[4,4,4-trifluoro-3-hydroxy-3-(1*H*-indol-2-ylmethyl)-1,1-dimethylbutyl]phenol;

2-[3-(6,7-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-4,4,4-trifluoro-3-hydroxy-1,1-dimethylbutyl]-4-fluorophenol;

2-(7-Chloro-5-trifluoromethyl-1*H*-benzoimidazol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

2-(5,7-Dimethyl-1*H*-benzoimidazol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-(5-fluoro-2-methylphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-(4-fluorophenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-(3-fluorophenyl)-4-methylpentan-2-ol;

2-[3-(5,7-Dimethyl-1*H*-benzoimidazol-2-ylmethyl)-4,4,4-trifluoro-3-hydroxy-1,1-dimethylbutyl]-4-fluorophenol;

1,1,1-Trifluoro-4-(3-methoxyphenyl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-(3-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-4-methyl-2-(4-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-4-methyl-2-(4-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorophenyl)-4-methyl-2-(4-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-methyl-2-quinolin-4-ylmethyl-4-(3-trifluoromethylphenyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-4-methyl-2-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-4-methyl-2-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorophenyl)-4-methyl-2-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-4-methyl-2-(7-methyl-1*H*-benzoimidazol-2-ylmethyl)pentan-2-ol;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-3*H*-benzoimidazole-5-carbonitrile;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-(3-trifluoromethylphenyl)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

5-Fluoro-2-(4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)butyl]phenol;

4-(5-Bromo-4-fluoro-2-methoxyphenyl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

2-(6-Chloro-4-methyl-1*H*-indol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

2-(2-Phenyl-4-methylimidazol-1-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihydrobenzofuran-7-yl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

2-(2-Phenylimidazol-1-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihydrobenzofuran-7-yl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-methyl-4-(5-methyl-2,3-dihydrobenzofuran-7-yl)-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-phenylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-(5-methyl-2,3-dihydrobenzofuran-7-yl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(7-fluoro-4-methyl-1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-*m*-tolylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-naphthalen-2-ylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-*o*-tolylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-*p*-tolylpentan-2-ol;

4-(2,3-Dihydrobenzofuran-5-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(7-Bromo-2,3-dihydrobenzofuran-5-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(2,3-Dihydrobenzofuran-5-yl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(1-methoxynaphthalen-2-yl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

2-(4,4,4-Trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)naphthalen-1-ol;

1,1,1-Trifluoro-4-methyl-4-naphthalen-2-yl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-7-carbonitrile;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-(1-methoxynaphthalen-2-yl)-4-methylpentan-2-ol;

2-[4,4,4-Trifluoro-3-hydroxy-3-(1*H*-indol-2-ylmethyl)-1,1-dimethylbutyl]naphthalen-1-ol;

1,1,1-Trifluoro-4-methyl-2-quinolin-4-ylmethyl-4-*p*-tolylpentan-2-ol;

4-Chroman-8-yl-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-4-methyl-4-phenyl-2-quinolin-4-ylmethylpentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)butyl]phenol;

4-(6-Bromochroman-8-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)butyl]phenol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*b*]pyridin-2-ylmethyl)pentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[3,2-*b*]pyridin-2-ylmethyl)butyl]phenol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*b*]pyridin-2-ylmethyl)pentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[2,3-*b*]pyridin-2-ylmethyl)butyl]phenol;

1,1,1-Trifluoro-4-(3-fluorophenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-methyl-4-phenyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(7-fluoroquinolin-4-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-2-(7-fluoroquinolin-4-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-2-(5-fluoroquinolin-4-ylmethyl)-4-methylpentan-2-ol;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

2-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

2-[4-(5-Fluoro-2-methylphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

1,1,1-Trifluoro-4-(2-methoxyphenyl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-(2-methoxyphenyl)-4-methylpentan-2-ol;

2-[4-(5-Fluoro-2,3-dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

4-(5-Bromo-2-methoxyphenyl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(5-Bromo-2-methoxyphenyl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-(4,4,4-Trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

1,1,1-Trifluoro-4-methyl-4-phenyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-[4-(5-Bromo-2,3-dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

4-Bromo-2-(4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

2-[4-(4-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethyl-pentyl]-1*H*-indole-3-carbonitrile;

2-(2-Hydroxy-4-methyl-4-phenyl-2-trifluoromethylpentyl)-4-methyl-1*H*-indole-6-carbonitrile;

2-[4-(3-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

2-[4-(4-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

2-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-methyl-4-phenyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-(2-Hydroxy-4-methyl-4-phenyl-2-trifluoromethylpentyl)-1*H*-indole-5-carbonitrile;

2-[4-(3-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

2-[4-(4-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-(5,6,7,8-tetrahydroquinolin-4-ylmethyl)pentan-2-ol;

1-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-(2-Hydroxy-4-methyl-4-phenyl-2-trifluoromethylpentyl)-1*H*-indole-3-carbonitrile;

5-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)butyl]phenol;

2-[4-(4-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(3-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(4-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(5-Fluoro-2-methylphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-(4-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-methyl-4-phenylpentan-2-ol;

2-[4-(4-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carboxylic acid methyl ester;

1-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(3-methyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(3-methoxyphenyl)-4-methyl-2-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

2-[2-Hydroxy-4-(3-methoxyphenyl)-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

5-Fluoro-2-[4,4,4-trifluoro-3-(7-fluoro-1*H*-indol-2-ylmethyl)-3-hydroxy-1,1-dimethylbutyl]phenol;

2-[4-(5-Fluoro-2-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(3-methyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)butyl]phenol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-thiophen-3-ylpentan-2-ol;

1,1,1-Trifluoro-4-methyl-2-quinolin-4-ylmethyl-4-thiophen-3-ylpentan-2-ol;

5-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)butyl]phenol;

1,1,1-Trifluoro-4-(3-fluorophenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-[4-(4-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

3-(4,4,4-Trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(4-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

4-(5-Bromo-2-methoxyphenyl)-1,1,1-trifluoro-4-methyl-2-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

2-[4-(5-Bromo-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(5-Bromo-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carboxylic acid methyl ester;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carboxylic acid methyl ester;

4-(2,6-Dimethylphenyl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

3-[4,4,4-Trifluoro-3-hydroxy-3-(1*H*-indol-2-ylmethyl)-1,1-dimethylbutyl]phenol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihydrobenzofuran-7-yl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol; and

1-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carboxylic acid methyl ester,

or a tautomer, prodrug, solvate, or salt thereof.

More preferred compounds of Formula (IA) include the following:

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-(2,6-Dichloropyridin-4-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-[3-(2,6-Dichloropyridin-4-ylmethyl)-4,4,4-trifluoro-3-hydroxy-1,1-dimethylbutyl]-4-fluorophenol;

4-(5-Bromo-2,3-dihydrobenzofuran-7-yl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-(1*H*-Benzimidazol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorophenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(quinolin-4-ylmethyl)pentan-2-ol;

4-(2,3-dihydro-5-cyanobenzofuran-7-yl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(2-chloropyridin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-hydroxyphenyl)-4-methyl-2-(2-chloropyridin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(2-chloroquinolin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-hydroxyphenyl)-4-methyl-2-(2-chloroquinolin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-(4-methoxyphenyl)-4-methylpentan-2-ol;

4-[4,4,4-Trifluoro-3-hydroxy-3-(1*H*-indol-2-ylmethyl)-1,1-dimethylbutyl]phenol;

1,1,1-Trifluoro-2-(5-fluoro-1*H*-indol-2-ylmethyl)-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

4-(2,3-dihydrobenzofuran-7-yl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(2-bromopyridin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(7-methyl-1*H*-benzoimidazol-2-ylmethyl)pentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(4-methyl-1*H*-indol-2-ylmethyl)butyl]phenol;

4-Fluoro-2-[4,4,4-trifluoro-3-(7-fluoro-1*H*-indol-2-ylmethyl)-3-hydroxy-1,1-dimethylbutyl]phenol;

1,1,1-Trifluoro-2-(6-fluoro-1*H*-benzoimidazol-2-ylmethyl)-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

2-(6,7-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(5-Bromo-2,3-dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(3-Ethyl-2-methoxyphenyl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

2-Ethyl-6-(4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

2-Ethyl-6-[4,4,4-trifluoro-3-hydroxy-3-(1*H*-indol-2-ylmethyl)-1,1-dimethylbutyl]phenol;

2-(5,7-Dimethyl-1*H*-benzoimidazol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

2-[3-(5,7-Dimethyl-1*H*-benzoimidazol-2-ylmethyl)-4,4,4-trifluoro-3-hydroxy-1,1-dimethylbutyl]-4-fluorophenol;

1,1,1-Trifluoro-4-(3-methoxyphenyl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-(3-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-4-methyl-2-(4-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-4-methyl-2-(4-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorophenyl)-4-methyl-2-(4-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-methyl-2-quinolin-4-ylmethyl-4-(3-trifluoromethylphenyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-4-methyl-2-(7-methyl-1*H*-benzoimidazol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-(3-trifluoromethylphenyl)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

5-Fluoro-2-(4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

4-(5-Bromo-4-fluoro-2-methoxyphenyl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

2-(2-Phenyl-4-methylimidazol-1-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihydrobenzofuran-7-yl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

2-(2-Phenylimidazol-1-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihydrobenzofuran-7-yl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-methyl-4-(5-methyl-2,3-dihydrobenzofuran-7-yl)-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-phenylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-(5-methyl-2,3-dihydrobenzofuran-7-yl)pentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-*m*-tolylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-naphthalen-2-ylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-*o*-tolylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-*p*-tolylpentan-2-ol;

4-(2,3-Dihydrobenzofuran-5-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(7-Bromo-2,3-dihydrobenzofuran-5-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(2,3-Dihydrobenzofuran-5-yl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(1-methoxynaphthalen-2-yl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

2-(4,4,4-Trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)naphthalen-1-ol;

1,1,1-Trifluoro-4-methyl-4-naphthalen-2-yl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-(1-methoxynaphthalen-2-yl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-methyl-2-quinolin-4-ylmethyl-4-*p*-tolylpentan-2-ol;

4-Chroman-8-yl-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-4-methyl-4-phenyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(6-Bromochroman-8-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*b*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*b*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorophenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-methyl-4-phenyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(7-fluoroquinolin-4-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-2-(7-fluoroquinolin-4-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-2-(5-fluoroquinolin-4-ylmethyl)-4-methylpentan-2-ol;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

2-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

2-[4-(5-Fluoro-2-methylphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

1,1,1-Trifluoro-4-(2-methoxyphenyl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-(2-methoxyphenyl)-4-methylpentan-2-ol;

2-[4-(5-Fluoro-2,3-dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

4-(5-Bromo-2-methoxyphenyl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(5-Bromo-2-methoxyphenyl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-(4,4,4-Trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

1,1,1-Trifluoro-4-methyl-4-phenyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-[4-(5-Bromo-2,3-dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

4-Bromo-2-(4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-[4-(4-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethyl-pentyl]-1*H*-indole-3-carbonitrile;

2-(2-Hydroxy-4-methyl-4-phenyl-2-trifluoromethylpentyl)-4-methyl-1*H*-indole-6-carbonitrile;

2-[4-(3-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

2-[4-(4-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

2-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-methyl-4-phenyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-(2-Hydroxy-4-methyl-4-phenyl-2-trifluoromethylpentyl)-1*H*-indole-5-carbonitrile;

2-[4-(3-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

2-[4-(4-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-(5,6,7,8-tetrahydroquinolin-4-ylmethyl)pentan-2-ol;

1-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-(2-Hydroxy-4-methyl-4-phenyl-2-trifluoromethylpentyl)-1*H*-indole-3-carbonitrile;

5-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)butyl]phenol;

2-[4-(4-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(3-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(4-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(5-Fluoro-2-methylphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)butyl]phenol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-methyl-4-phenylpentan-2-ol;

2-[4-(4-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carboxylic acid methyl ester;

1-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(3-methyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(3-methoxyphenyl)-4-methyl-2-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

2-[2-Hydroxy-4-(3-methoxyphenyl)-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)butyl]phenol;

5-Fluoro-2-[4,4,4-trifluoro-3-(7-fluoro-1*H*-indol-2-ylmethyl)-3-hydroxy-1,1-dimethylbutyl]phenol;

2-[4-(5-Fluoro-2-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(3-methyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)butyl]phenol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-thiophen-3-ylpentan-2-ol;

1,1,1-Trifluoro-4-methyl-2-quinolin-4-ylmethyl-4-thiophen-3-ylpentan-2-ol;

5-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)butyl]phenol;

1,1,1-Trifluoro-4-(3-fluorophenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

3-(4,4,4-Trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

2-[4-(5-Bromo-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carboxylic acid methyl ester;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carboxylic acid methyl ester;

4-(2,6-Dimethylphenyl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

3-[4,4,4-Trifluoro-3-hydroxy-3-(1*H*-indol-2-ylmethyl)-1,1-dimethylbutyl]phenol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihydrobenzofuran-7-yl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-[2-Hydroxy-4-(3-methoxyphenyl)-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

2-[4-(5-Bromo-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

2-[4-(4-Fluoro-2-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(5-nitro-1*H*-indol-2-ylmethyl)pentan-2-ol;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carboxylic acid amide;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carboxylic acid dimethylamide;

{2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indol-5-yl}morpholin-4-ylmethanone;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-6-carboxylic acid methyl ester;

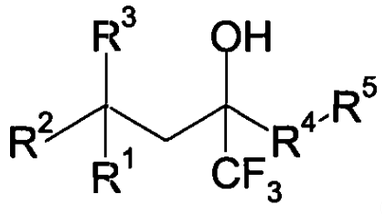
2-[4-(5-Fluoro-2-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-6-carboxylic acid methyl ester;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-6-carboxylic acid; and

2-[4-(5-Fluoro-2-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-6-carboxylic acid,

or a tautomer, prodrug, solvate, or salt thereof.

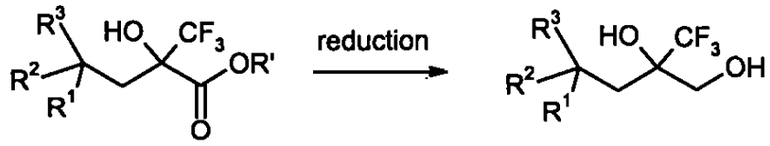
The invention also provides a method of making a compound of Formula (IA)



(IA)

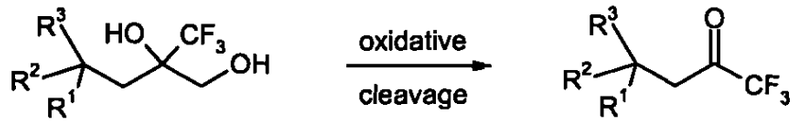
where R^1, R^2, R^3, R^4, and R^5 are as defined above, the method comprising:

(a) reacting an ester of Formula (II) with a suitable reducing agent in a suitable solvent to form a diol of Formula (III)



II III ;

(b) reacting the diol of Formula (III) under suitable oxidative cleavage conditions to form a ketone of Formula (IV)



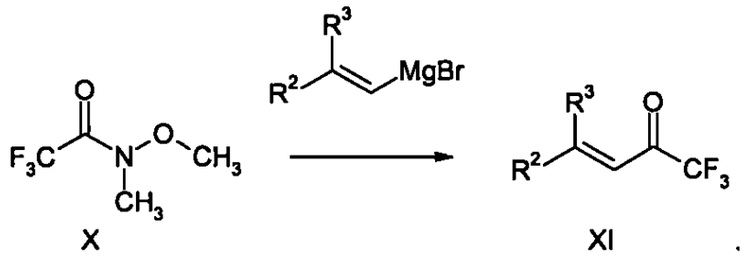
III IV ; and

(c) reacting the ketone of Formula (IV) with a suitable organometallic reagent R^5R^4M where M is Li or MgX and X is Cl, Br, or I, in a suitable solvent to form the compound of Formula (IA)



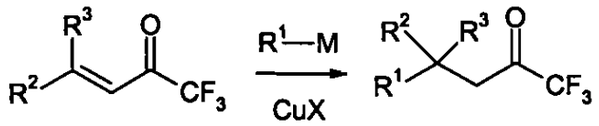
IV IA ; or

(a') reacting the trifluoroacetamide of Formula (X) with a vinyl magnesium bromide bearing R^2 and R^3 in a suitable solvent to provide the trifluoromethylenone of Formula (XI)



X XI ;

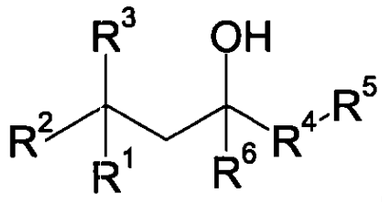
(b') reacting the trifluoromethylenone of Formula (XI) with a suitable organocopper reagent generated from an organometallic reagent R^5R^4M where M is Li or MgX and a copper salt CuX, where X is Cl, Br, or I, in a suitable solvent to form the ketone of Formula (IV)



XI IV ;

and performing step (c) as set forth above.

The instant invention is also directed to compounds of Formula (IB)



(IB)

wherein:

R^1 is an aryl or heteroaryl group, each optionally independently substituted with one to three substituent groups,

wherein each substituent group of R^1 is independently C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, C_3-C_8 cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_5 alkoxy, C_2-C_5 alkenyloxy, C_2-C_5 alkynyloxy, aryloxy, acyl, C_1-C_5 alkoxycarbonyl, C_1-C_5 alkanoyloxy, C_1-C_5 alkanoyl, aroyl, aminocarbonyl, C_1-C_5 alkylaminocarbonyl, C_1-C_5 dialkylaminocarbonyl, aminocarbonyloxy, C_1-C_5 alkylaminocarbonyloxy, C_1-C_5 dialkylaminocarbonyloxy, C_1-C_5 alkanoylamino, C_1-C_5 alkoxycarbonylamino, C_1-C_5 alkylsulfonylamino, aminosulfonyl, C_1-C_5 alkylaminosulfonyl, C_1-C_5 dialkylaminosulfonyl, halogen, hydroxy, carboxy, cyano, trifluoromethyl, trifluoromethoxy, nitro, or amino wherein the nitrogen atom is optionally independently mono- or di-substituted by C_1-C_5 alkyl or aryl; or ureido wherein either nitrogen atom is optionally independently substituted with C_1-C_5 alkyl; or C_1-C_5 alkylthio wherein the sulfur atom is optionally oxidized to a sulfoxide or sulfone,

wherein each substituent group of R^1 is optionally independently substituted with one to three substituent groups selected from methyl, methoxy, halogen, hydroxy, oxo, cyano, or amino,

R^2 and R^3 are each independently C_1-C_5 alkyl;

R^4 is C_1-C_5 alkyl, C_2-C_5 alkenyl, or C_2-C_5 alkynyl, each optionally independently substituted with one to three substituent groups,

wherein each substituent group of R^4 is independently C_1-C_3 alkyl, hydroxy, halogen, or oxo;

R^5 is a heteroaryl group optionally independently substituted with one to three substituent groups,

wherein each substituent group of R^5 is independently C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, C_3-C_8 cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_5 alkoxy, C_2-C_5 alkenyloxy, C_2-C_5 alkynyloxy, aryloxy, acyl, C_1-C_5 alkoxycarbonyl, C_1-C_5 alkanoyloxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, aminocarbonyloxy, C_1-C_5 alkylaminocarbonyloxy, C_1-C_5 dialkylaminocarbonyloxy, C_1-C_5 alkanoylamino, C_1-C_5 alkoxycarbonylamino, C_1-C_5 alkylsulfonylamino, C_1-C_5 alkylaminosulfonyl, C_1-C_5 dialkylaminosulfonyl, halogen, hydroxy, carboxy, cyano, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, nitro, or amino wherein the nitrogen atom is optionally independently mono- or di-substituted by C_1-C_5 alkyl; or ureido wherein either nitrogen atom is optionally independently substituted with C_1-C_5 alkyl; or C_1-C_5 alkylthio wherein the sulfur atom is optionally oxidized to a sulfoxide or sulfone,

wherein each substituent group of R^5 is optionally independently substituted with one to three substituent groups selected from C_1-C_3 alkyl, C_1-C_3 alkoxy, halogen, hydroxy, oxo, cyano, amino, or trifluoromethyl; and

R^6 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, carbocycle, heterocyclyl, aryl, heteroaryl, carbocycle-C_1-C_8 alkyl, aryl-C_1-C_8 alkyl, aryl-C_1-C_8 haloalkyl, heterocyclyl-C_1-C_8 alkyl, heteroaryl-C_1-C_8 alkyl, carbocycle-C_2-C_8 alkenyl, aryl-C_2-C_8 alkenyl, heterocyclyl-C_2-C_8 alkenyl, or heteroaryl-C_2-C_8 alkenyl, each optionally independently substituted with one to three substituent groups,

wherein each substituent group of R^6 is independently C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, C_3-C_8 cycloalkyl, phenyl, C_1-C_5 alkoxy, phenoxy, C_1-C_5 alkanoyl, aroyl, C_1-C_5 alkoxycarbonyl, C_1-C_5 alkanoyloxy, aminocarbonyloxy, C_1-C_5 alkylaminocarbonyloxy, C_1-C_5 dialkylaminocarbonyloxy, aminocarbonyl, C_1-C_5 alkylaminocarbonyl, C_1-C_5 dialkylaminocarbonyl, C_1-C_5 alkanoylamino, C_1-C_5 alkoxycarbonylamino, C_1-C_5 alkylsulfonylamino, C_1-C_5 alkylaminosulfonyl, C_1-C_5 dialkylaminosulfonyl, halogen, hydroxy, carboxy, cyano, oxo, trifluoromethyl, nitro, amino wherein the nitrogen atom is optionally independently mono- or di-substituted by C_1-C_5 alkyl; or ureido wherein either nitrogen atom is optionally independently substituted with C_1-C_5 alkyl; or C_1-C_5 alkylthio wherein the sulfur atom is optionally oxidized to a sulfoxide or sulfone,

wherein R^6 cannot be trifluoromethyl,

or a tautomer, prodrug, solvate, or salt thereof.

Another aspect of the invention includes compounds of Formula (IB), wherein:

R^1 is thienyl, phenyl, naphthyl, dihydrobenzofuranyl, benzofuranyl, chromanyl, dihydroindolyl, indolyl, dihydrobenzothienyl, benzothienyl, benzodioxolanyl, benzoxazolyl, benzisoxazolyl, benzpyrazolyl, benzimidazolyl, quinolinyl, pyridinyl, pyrimidinyl, or pyrazinyl, each optionally independently substituted with one to three substituent groups,

wherein each substituent group of R^1 is independently C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, C_1-C_3 alkoxy, C_2-C_3 alkenyloxy, C_1-C_3 alkanoyl, C_1-C_3 alkoxycarbonyl, C_1-C_3

alkanoyloxy, halogen, hydroxy, carboxy, cyano, trifluoromethyl, nitro, or C_1-C_3 alkylthio wherein the sulfur atom is optionally oxidized to a sulfoxide or sulfone,

wherein each substituent group of R^1 is optionally independently substituted with a substituent group selected from methyl, methoxy, halogen, hydroxy, oxo, cyano, or amino;

R^2 and R^3 are each independently C_1-C_3 alkyl;

R^4 is CH_2;

R^5 is an imidazolyl, pyridyl, indolyl, azaindolyl, diazaindolyl, benzofuranyl, furanopyridinyl, furanopyrimidinyl, benzothienyl, thienopyridinyl, thienopyrimidinyl, benzoxazolyl, oxazolopyridinyl, benzothiazolyl, thiazolopyridinyl, benzimidazolyl, imidazolopyridinyl, quinolinyl, or isoquinolinyl group, each optionally independently substituted with one to three substituent groups,

wherein each substituent group of R^5 is independently C_1-C_3 alkyl, C_2-C_3 alkenyl, phenyl, C_1-C_3 alkoxy, methoxycarbonyl, aminocarbonyl, C_1-C_3 alkylaminocarbonyl, C_1-C_3 dialkylaminocarbonyl, heterocyclylcarbonyl, fluoro, chloro, bromo, cyano, trifluoromethyl, or C_1-C_3 alkylthio wherein the sulfur atom is optionally oxidized to a sulfoxide or sulfone,

wherein each substituent group of R^5 is optionally independently substituted with a substituent group selected from methyl, methoxy, fluoro, chloro, bromo, or trifluoromethyl; and

R^6 is C_1-C_5 alkyl, C_2-C_5 alkenyl, C_3-C_6 cycloalkyl, phenyl, C_3-C_6 cycloalkyl-C_1-C_3 alkyl, phenyl-C_1-C_3 alkyl, phenyl-C_1-C_3 haloalkyl, C_3-C_6 cycloalkyl-C_2-C_3 alkenyl, phenyl-C_2-C_3 alkenyl, each optionally independently substituted with one to three substituent groups,

wherein each substituent group of R^6 is independently C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, C_1-C_3 alkoxy, aminocarbonyl, C_1-C_3 alkylaminocarbonyl, C_1-C_3 dialkylaminocarbonyl, halogen, hydroxy, carboxy, cyano, trifluoromethyl, nitro, or C_1-C_3 alkylthio wherein the sulfur atom is optionally oxidized to a sulfoxide or sulfone,

or a tautomer, prodrug, solvate, or salt thereof.

Yet another aspect of the invention includes compounds of Formula (IB), wherein:

R^1 is thienyl, phenyl, naphthyl, pyridyl, chromanyl, dihydrobenzofuranyl, or benzofuranyl, each optionally independently substituted with one or two substituent groups,

wherein each substituent group of R^1 is independently methyl, ethyl, methoxy, ethoxy, fluoro, chloro, bromo, hydroxy, trifluoromethyl, or cyano;

R^2 and R^3 are each methyl;

R^4 is CH_2;

R^5 is a pyridyl, indolyl, azaindolyl, benzofuranyl, furanopyridinyl, thienopyridinyl, benzoxazolyl, benzimidazolyl, quinolinyl, or isoquinolinyl group, each optionally independently substituted with one to three substituent groups,

wherein each substituent group of R^5 is independently methyl, phenyl, methoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminoaminocarbonyl, morpholinylcarbonyl, fluoro, chloro, bromo, cyano, or trifluoromethyl; and

R^6 is C_1-C_5 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl-methyl-, or benzyl, each optionally independently substituted with one to three substituent groups,

wherein each substituent group of R^6 is independently methyl, methoxy, fluoro, chloro, bromo, cyano, trifluoromethyl, or hydroxy,

or a tautomer, prodrug, solvate, or salt thereof.

Yet another aspect of the invention includes compounds of Formula (IB), wherein:

R^1 is phenyl, dihydrobenzofuranyl, or benzofuranyl, each optionally independently substituted with one to three substituent groups,

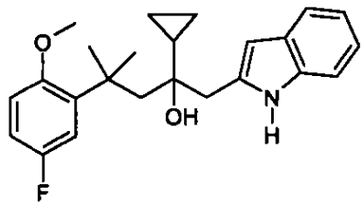
wherein each substituent group of R^1 is independently C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, C_1-C_3 alkoxy, C_2-C_3 alkenyloxy, C_1-C_3 alkanoyl, C_1-C_3 alkoxycarbonyl, C_1-C_3 alkanoyloxy, halogen, hydroxy, carboxy, cyano, trifluoromethyl, nitro, or C_1-C_3 alkylthio wherein the sulfur atom is optionally oxidized to a sulfoxide or sulfone; and

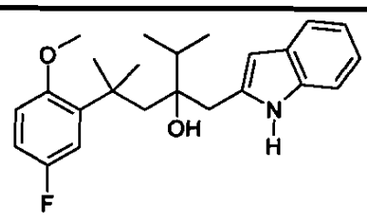
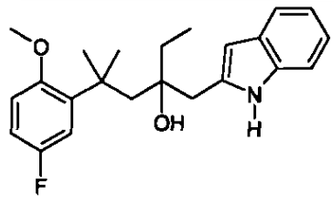
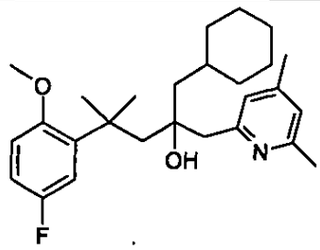
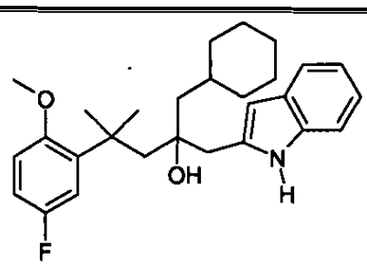
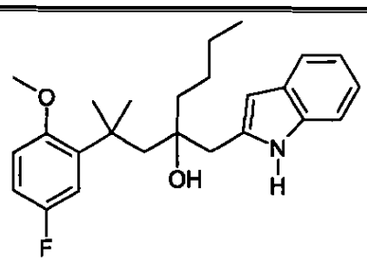
R^2 and R^3 are each independently C_1-C_3 alkyl,

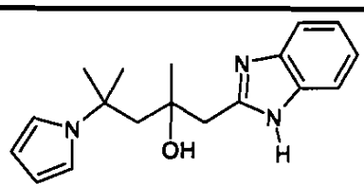
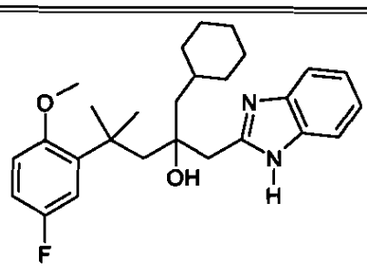
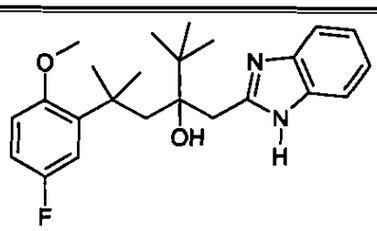
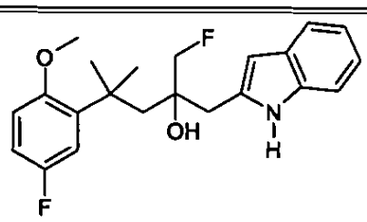
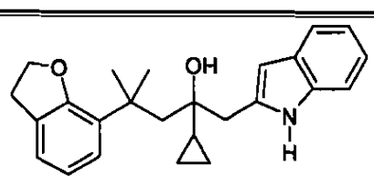
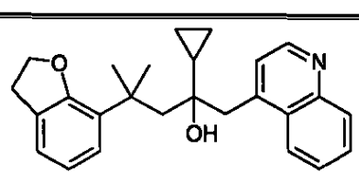
or a tautomer, prodrug, solvate, or salt thereof.

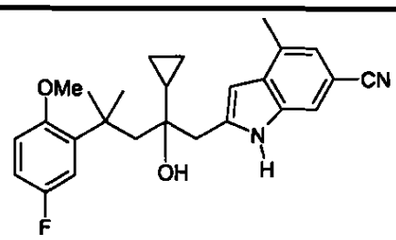
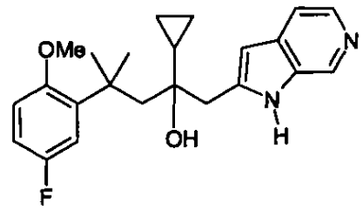
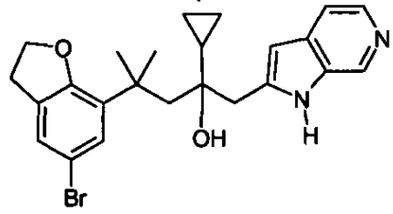
In yet other aspects of the invention, one to three substituent groups of R^1 in the compounds of Formula (IB) is independently C_1-C_3 alkylamino or C_1-C_3 dialkylamino.

The following are representative compounds of Formula (IB) according to the invention:

Compound Name	Compound Structure
2-Cyclopropyl-4-(5-fluoro-2-methoxyphenyl)-1-(1*H*-indol-2-yl)-4-methylpentan-2-ol	

5-(5-Fluoro-2-methoxyphenyl)-3-(1*H*-indol-2-ylmethyl)-2,5-dimethylhexan-3-ol	
5-(5-Fluoro-2-methoxyphenyl)-3-(1*H*-indol-2-ylmethyl)-5-methylhexan-3-ol	
2-Cyclohexylmethyl-1-(4,6-dimethylpyridin-2-yl)-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol	
2-Cyclohexylmethyl-4-(5-fluoro-2-methoxyphenyl)-1-(1*H*-indol-2-yl)-4-methylpentan-2-ol	
7-(5-Fluoro-2-methoxyphenyl)-5-(1*H*-indol-2-ylmethyl)-7-methyloctan-5-ol	

2-(Benzimidazol-2-ylmethyl)-4-methyl-4-(pyrrol-1-yl)pentan-2-ol	
1-(1*H*-Benzoimidazol-2-yl)-2-cyclohexylmethyl-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol	
5-(5-Fluoro-2-methoxyphenyl)-3-(benzimidazol-2-ylmethyl)-2,2,5-trimethylhexan-3-ol	
4-(5-Fluoro-2-methoxyphenyl)-2-fluoromethyl-1-(1*H*-indol-2-yl)-4-methylpentan-2-ol	
2-Cyclopropyl-4-(2,3-dihydrobenzofuran-7-yl)-1-(1*H*-indol-2-yl)-4-methylpentan-2-ol	
2-Cyclopropyl-4-(2,3-dihydrobenzofuran-7-yl)-1-(quinolin-4-yl)-4-methylpentan-2-ol	

2-Cyclopropyl-4-(5-fluoro-2-methoxyphenyl)-1-(6-cyano-4-methylindol-2-yl)-4-methylpentan-2-ol	
2-Cyclopropyl-4-(5-fluoro-2-methoxyphenyl)-4-methyl-1-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)pentan-2-ol	
4-(5-Bromo-2,3-dihydrobenzofuran-7-yl)-2-cyclopropyl-4-methyl-1-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)pentan-2-ol	
or a tautomer, prodrug, solvate, or salt thereof.	

Preferred compounds of Formula (IB) include the following:

2-Cyclopropyl-4-(5-fluoro-2-methoxyphenyl)-1-(1*H*-indol-2-yl)-4-methylpentan-2-ol;

5-(5-Fluoro-2-methoxyphenyl)-3-(indol-2-ylmethyl)-2,5-dimethylhexan-3-ol;

5-(5-Fluoro-2-methoxyphenyl)-3-(indol-2-ylmethyl)-5-methylhexan-3-ol;

1-Cyclohexyl-4-(5-fluoro-2-methoxyphenyl)-2-(indol-2-ylmethyl)-4-methylpentan-2-ol;

5-(5-Fluoro-2-methoxyphenyl)-3-(benzimidazol-2-ylmethyl)-2,2,5-trimethylhexan-3-ol;

4-(5-Fluoro-2-methoxyphenyl)-2-fluoromethyl-1-(1*H*-indol-2-yl)-4-methylpentan-2-ol;

2-Cyclopropyl-4-(2,3-dihydrobenzofuran-7-yl)-1-(1*H*-indol-2-yl)-4-methylpentan-2-ol;

2-Cyclopropyl-4-(2,3-dihydrobenzofuran-7-yl)-1-(quinolin-4-yl)-4-methylpentan-2-ol;

2-Cyclopropyl-4-(5-fluoro-2-methoxyphenyl)-1-(6-cyano-4-methylindol-2-yl)-4-methylpentan-2-ol;

2-Cyclopropyl-4-(5-fluoro-2-methoxyphenyl)-4-methyl-1-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)pentan-2-ol; and

4-(5-Bromo-2,3-dihydrobenzofuran-7-yl)-2-cyclopropyl-4-methyl-1-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)pentan-2-ol,

or a tautomer, prodrug, solvate, or salt thereof.

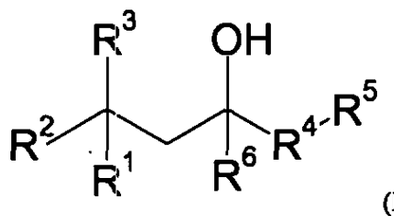
More preferred compounds of Formula (IB) include:

2-Cyclopropyl-4-(2,3-dihydrobenzofuran-7-yl)-1-(1*H*-indol-2-yl)-4-methylpentan-2-ol; and

2-Cyclopropyl-4-(5-fluoro-2-methoxyphenyl)-4-methyl-1-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)pentan-2-ol;

or a tautomer, prodrug, solvate, or salt thereof.

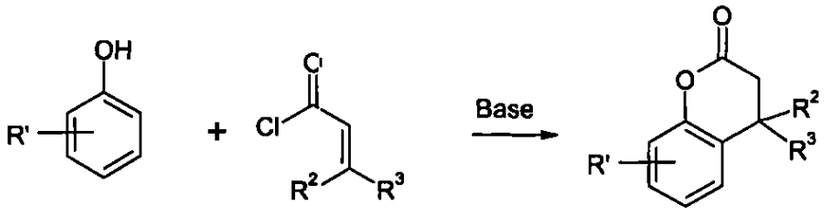
The invention further provides methods of making a compound of Formula (IB). One method of making a compound of Formula (IB)



(IB)

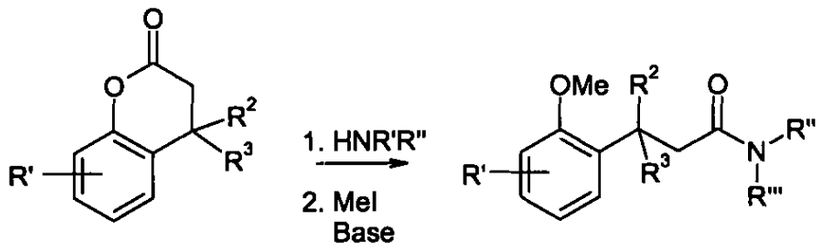
where R^1 is an optionally substituted 2-methoxyphenyl group and R^2, R^3, R^4, R^5, and R^6 are as defined above, the method comprising:

(a) reacting an optionally substituted phenol of Formula (XXII) with an acryloyl chloride of Formula (XIII) in the presence of a suitable base, followed by cyclization of the intermediate ester by treatment with a suitable Lewis acid to form a lactone of Formula (XIV)



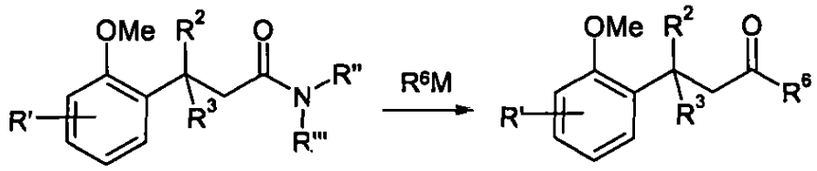
XII XIII XIV ;

(b) reacting the lactone of Formula (XIV) with a suitable amine HNR'R'', followed by treatment of the intermediate phenol with methyl iodide in the presence of a suitable base to form an amide of Formula (XV)



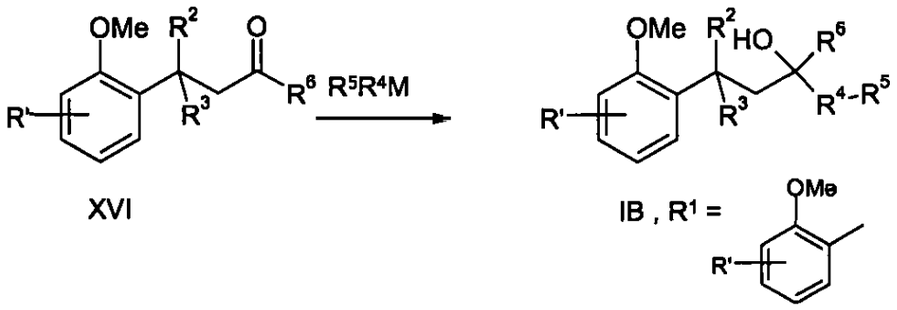
XIV XV ;

(c) reacting the amide of Formula (XV) with a suitable organometallic reagent R^6M, where M is Li or MgX and X is Cl, Br, or I, in a suitable solvent to form a ketone of Formula (XVI)



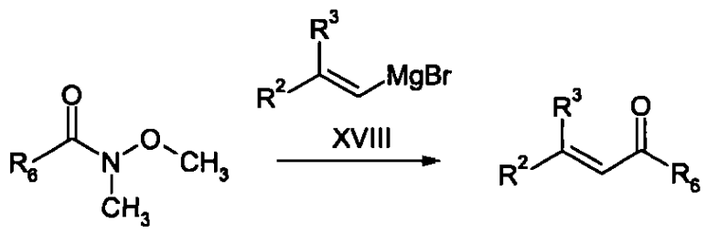
XV XVI ;

(d) reacting the ketone of Formula (XVI) with a suitable organometallic reagent R^5R^4M where M is Li or MgX and X is Cl, Br, or I, in a suitable solvent to form the compound of Formula (IB)



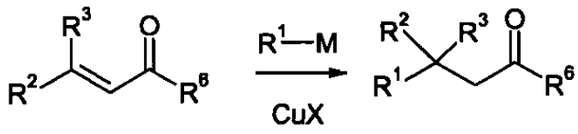
A second method for making a compound of Formula (IB) comprises:

(a') reacting an amide of Formula (XVII) with a vinyl magnesium bromide bearing R^2 and R^3 of Formula (XVIII) in a suitable solvent to provide an enone of Formula (XIX)



XVII XIX ;

(b') reacting the enone of Formula (XIX) with a suitable organocopper reagent generated from an organometallic reagent R^1M, where M is Li or MgX, and a copper salt CuX, where X is Cl, Br, or I, in a suitable solvent to form a ketone of Formula (XX)



XIX XX ; and

(c') reacting the ketone of Formula (XX) with a suitable organometallic reagent R^5R^4M, where M is Li or MgX, and X is Cl, Br, or I, in a suitable solvent to form the compound of Formula (IB)



XX IB

In another aspect of the invention, the compounds according to the invention are formulated into pharmaceutical compositions comprising an effective amount, preferably a pharmaceutically effective amount, of a compound according to the invention or a tautomer, prodrug, solvate, or salt thereof, and a pharmaceutically acceptable excipient or carrier.

The invention also provides a method of modulating the glucocorticoid receptor function in a patient, the method comprising administering to the patient an effective amount of a compound according to the invention or a tautomer, prodrug, solvate, or salt thereof.

The invention further provides a method of treating a disease-state or condition mediated by the glucocorticoid receptor function in a patient in need of such treatment, the method comprising administering to the patient an effective amount of a pharmaceutically acceptable compound according to the invention or a tautomer, prodrug, solvate, or salt thereof.

In addition, the invention also provides a method of treating a disease-state or condition selected from: type II diabetes, obesity, cardiovascular diseases, hypertension, arteriosclerosis, neurological diseases, adrenal and pituitary tumors, and glaucoma, in a patient in need of such treatment, the method comprising administering to the patient an effective amount of a

pharmaceutically acceptable compound according to the invention or a tautomer, prodrug, solvate, or salt thereof.

The invention provides a method of treating a disease characterized by inflammatory, allergic, or proliferative processes, in a patient in need of such treatment, the method comprising administering to the patient an effective amount of a pharmaceutically acceptable compound according to the invention or a tautomer, prodrug, solvate, or salt thereof. In a preferred embodiment of the invention, the disease characterized by inflammatory, allergic, or proliferative processes is selected from: (i) lung diseases; (ii) rheumatic diseases or autoimmune diseases or joint diseases; (iii) allergic diseases; (iv) vasculitis diseases; (v) dermatological diseases; (vi) renal diseases; (vii) hepatic diseases; (viii) gastrointestinal diseases; (ix) proctological diseases; (x) eye diseases; (xi) diseases of the ear, nose, and throat (ENT) area; (xii) neurological diseases; (xiii) blood diseases; (xiv) tumor diseases; (xv) endocrine diseases; (xvi) organ and tissue transplantations and graft-versus-host diseases; (xvii) severe states of shock; (xviii) substitution therapy; and (xix) pain of inflammatory genesis. In another preferred embodiment of the invention, the disease characterized by inflammatory, allergic, or proliferative processes is selected from: type I diabetes, osteoarthritis, Guillain-Barre syndrome, restenosis following percutaneous transluminal coronary angioplasty, Alzheimer disease, acute and chronic pain, atherosclerosis, reperfusion injury, bone resorption diseases, congestive heart failure, myocardial infarction, thermal injury, multiple organ injury secondary to trauma, acute purulent meningitis, necrotizing enterocolitis, and syndromes associated with hemodialysis, leukopheresis, and granulocyte transfusion.

The invention further provides methods of treating the disease-states or conditions mentioned above, in a patient in need of such treatment, the methods comprising sequentially or simultaneously administering to the patient: (a) an effective amount of a pharmaceutically acceptable compound according to the invention or a tautomer, prodrug, solvate, or salt thereof; and (b) a pharmaceutically acceptable glucocorticoid.

The invention further provides a method of assaying the glucocorticoid receptor function in a sample, comprising: (a) contacting the sample with a selected amount of a compound according to the invention or a tautomer, prodrug, solvate, or salt thereof; and (b) detecting the amount of

the compound according to the invention or a tautomer, prodrug, solvate, or salt thereof bound to glucocorticoid receptors in the sample. In a preferred embodiment of the invention, the compound according to the invention or a tautomer, prodrug, solvate, or salt thereof is labeled with a detectable marker selected from: a radiolabel, fluorescent tag, a chemiluminescent tag, a chromophore, and a spin label.

The invention also provides a method of imaging the glucocorticoid receptor distribution in a sample or patient, the method comprising: (a) contacting the sample or administering to a patient a compound according to the invention or a tautomer, prodrug, solvate, or salt thereof having a detectable marker; (b) detecting the spatial distribution and amount of the compound according to the invention or a tautomer, prodrug, solvate, or salt thereof having a detectable marker bound to glucocorticoid receptors in the sample or patient using an imaging means to obtain an image; and (c) displaying an image of the spatial distribution and amount of the compound according to the invention or a tautomer, prodrug, solvate, or salt thereof having a detectable marker bound to glucocorticoid receptors in the sample. In a preferred embodiment of the invention, the imaging means is selected from: radioscintigraphy, nuclear magnetic resonance imaging (MRI), computed tomography (CT scan), or positron emission tomography (PET).

The invention also provides a kit for the *in vitro* diagnostic determination of the glucocorticoid receptor function in a sample, comprising: (a) a diagnostically effective amount of a compound according to the invention or a tautomer, prodrug, solvate, or salt thereof; and (b) instructions for use of the diagnostic kit.

Detailed Description of the Invention

Definition of Terms and Conventions Used

Terms not specifically defined herein should be given the meanings that would be given to them by one of skill in the art in light of the disclosure and the context. As used in the specification and appended claims, however, unless specified to the contrary, the following terms have the meaning indicated and the following conventions are adhered to.

A. Chemical Nomenclature, Terms, and Conventions

In the groups, radicals, or moieties defined below, the number of carbon atoms is often specified preceding the group, for example, C_1-C_{10} alkyl means an alkyl group or radical having 1 to 10 carbon atoms. The term "lower" applied to any carbon-containing group means a group containing from 1 to 8 carbon atoms, as appropriate to the group (i.e., a cyclic group must have at least 3 atoms to constitute a ring). In general, for groups comprising two or more subgroups, the last named group is the radical attachment point, for example, "alkylaryl" means a monovalent radical of the formula Alk-Ar-, while "arylalkyl" means a monovalent radical of the formula Ar-Alk- (where Alk is an alkyl group and Ar is an aryl group). Furthermore, the use of a term designating a monovalent radical where a divalent radical is appropriate shall be construed to designate the respective divalent radical and *vice versa*. Unless otherwise specified, conventional definitions of terms control and conventional stable atom valences are presumed and achieved in all formulas and groups.

The terms "alkyl" or "alkyl group" mean a branched or straight-chain saturated aliphatic hydrocarbon monovalent radical. This term is exemplified by groups such as methyl, ethyl, *n*-propyl, 1-methylethyl (isopropyl), *n*-butyl, *n*-pentyl, 1,1-dimethylethyl (*tert*-butyl), and the like. It may be abbreviated "Alk".

The terms "alkenyl" or "alkenyl group" mean a branched or straight-chain aliphatic hydrocarbon monovalent radical containing at least one carbon-carbon double bond. This term is exemplified by groups such as ethenyl, propenyl, *n*-butenyl, isobutenyl, 3-methylbut-2-enyl, *n*-pentenyl, heptenyl, octenyl, decenyl, and the like.

The terms "alkynyl" or "alkynyl group" mean a branched or straight-chain aliphatic hydrocarbon monovalent radical containing at least one carbon-carbon triple bond. This term is exemplified by groups such as ethynyl, propynyl, *n*-butynyl, 2-butynyl, 3-methylbutynyl, *n*-pentynyl, heptynyl, octynyl, decynyl, and the like.

The terms "alkylene" or "alkylene group" mean a branched or straight-chain saturated aliphatic hydrocarbon divalent radical having the specified number of carbon atoms. This term is exemplified by groups such as methylene, ethylene, propylene, *n*-butylene, and the like, and may alternatively and equivalently be denoted herein as -(alkyl)-.

The terms "alkenylene" or "alkenylene group" mean a branched or straight-chain aliphatic hydrocarbon divalent radical having the specified number of carbon atoms and at least one carbon-carbon double bond. This term is exemplified by groups such as ethenylene, propenylene, *n*-butenylene, and the like, and may alternatively and equivalently be denoted herein as -(alkylenyl)-.

The terms "alkynylene" or "alkynylene group" mean a branched or straight-chain aliphatic hydrocarbon divalent radical containing at least one carbon-carbon triple bond. This term is exemplified by groups such as ethynylene, propynylene, *n*-butynylene, 2-butynylene, 3-methylbutynylene, *n*-pentynylene, heptynylene, octynylene, decynylene, and the like, and may alternatively and equivalently be denoted herein as -(alkynyl)-.

The terms "alkoxy" or "alkoxy group" mean a monovalent radical of the formula AlkO-, where Alk is an alkyl group. This term is exemplified by groups such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, *sec*-butoxy, *tert*-butoxy, pentoxy, and the like.

The terms "aryloxy", "aryloxy group", mean a monovalent radical of the formula ArO-, where Ar is aryl. This term is exemplified by groups such as phenoxy, naphthoxy, and the like.

The terms "alkylcarbonyl", "alkylcarbonyl group", "alkanoyl", or "alkanoyl group" mean a monovalent radical of the formula AlkC(O)-, where Alk is alkyl or hydrogen.

The terms "arylcarbonyl", "arylcarbonyl group", "aroyl" or "aroyl group" mean a monovalent radical of the formula ArC(O)-, where Ar is aryl.

The terms "acyl" or "acyl group" mean a monovalent radical of the formula RC(O)-, where R is a substituent selected from hydrogen or an organic substituent. Exemplary substituents include alkyl, aryl, arylalkyl, cycloalkyl, heterocyclyl, heteroaryl, heteroarylalkyl, and the like. As such, the terms comprise alkylcarbonyl groups and arylcarbonyl groups.

The terms "acylamino" or "acylamino group" mean a monovalent radical of the formula RC(O)N(R)-, where each R is a substituent selected from hydrogen or a substituent group.

The terms "alkoxycarbonyl" or "alkoxycarbonyl group" mean a monovalent radical of the formula AlkO-C(O)-, where Alk is alkyl. Exemplary alkoxycarbonyl groups include methoxycarbonyl, ethoxycarbonyl, *tert*-butyloxycarbonyl, and the like.

The terms "alkylaminocarbonyloxy" or "alkylaminocarbonyloxy group" mean a monovalent radical of the formula $R_2NC(O)O$-, where each R is independently hydrogen or lower alkyl.

The term "alkoxycarbonylamino" or "alkoxycarbonylamino group" mean a monovalent radical of the formula ROC(O)NH-, where R is lower alkyl.

The terms "alkylcarbonylamino" or "alkylcarbonylamino group" or "alkanoylamino" or "alkanoylamino groups" mean a monovalent radical of the formula AlkC(O)NH-, where Alk is alkyl. Exemplary alkylcarbonylamino groups include acetamido ($CH_3C(O)NH$-).

The terms "alkylaminocarbonyloxy" or "alkylaminocarbonyloxy group" mean a monovalent radical of the formula AlkNHC(O)O-, where Alk is alkyl.

The terms "amino" or "amino group" mean an $-NH_2$ group.

The terms "alkylamino" or "alkylamino group" mean a monovalent radical of the formula (Alk)NH-, where Alk is alkyl. Exemplary alkylamino groups include methylamino, ethylamino, propylamino, butylamino, *tert*-butylamino, and the like.

The terms "dialkylamino" or "dialkylamino group" mean a monovalent radical of the formula (Alk)(Alk)N-, where each Alk is independently alkyl. Exemplary dialkylamino groups include dimethylamino, methylethylamino, diethylamino, dipropylamino, ethylpropylamino, and the like.

The terms "substituted amino" or "substituted amino group" mean a monovalent radical of the formula $-NR_2$, where each R is independently a substituent selected from hydrogen or the specified substituents (but where both Rs cannot be hydrogen). Exemplary substituents include alkyl, alkanoyl, aryl, arylalkyl, cycloalkyl, heterocyclyl, heteroaryl, heteroarylalkyl, and the like.

The terms "alkoxycarbonylamino" or "alkoxycarbonylamino group" mean a monovalent radical of the formula AlkOC(O)NH-, where Alk is alkyl.

The terms "ureido" or "ureido group" mean a monovalent radical of the formula $R_2NC(O)NH-$, where each R is independently hydrogen or alkyl.

The terms "halogen" or "halogen group" mean a fluoro, chloro, bromo, or iodo group.

The term "halo" means one or more hydrogen atoms of the group are replaced by halogen groups.

The terms "haloalkyl" or "haloalkyl group" mean a branched or straight-chain saturated aliphatic hydrocarbon monovalent radical, wherein one or more hydrogen atoms thereof are each independently replaced with halogen atoms. This term is exemplified by groups such as chloromethyl, 1,2-dibromoethyl, 1,1,1-trifluoropropyl, 2-iodobutyl, 1-chloro-2-bromo-3-fluoropentyl, and the like.

The terms "sulfanyl", "sulfanyl group", "thioether", or "thioether group" mean a divalent radical of the formula -S-.

The terms "alkylthio" or "alkylthio group" mean a monovalent radical of the formula AlkS-, where Alk is alkyl. Exemplary groups include methylthio, ethylthio, *n*-propylthio, isopropylthio, *n*-butylthio, and the like.

The terms "sulfonyl" or "sulfonyl group" mean a divalent radical of the formula $-SO_2-$.

The terms "sulfonylamino" or "sulfonylamino group" mean a divalent radical of the formula $-SO_2NR-$, where R is a hydrogen or a substituent group.

The terms "aminosulfonyl" or "aminosulfonyl group" mean a monovalent radical of the formula NR_2SO_2-, where R is each independently a hydrogen or a substituent group.

The terms "carbocycle" or "carbocyclic group" mean a stable aliphatic 3- to 15-membered monocyclic or polycyclic monovalent or divalent radical consisting solely of carbon and hydrogen atoms which may comprise one or more fused or bridged ring(s), preferably a 5- to 7-membered monocyclic or 7- to 10-membered bicyclic ring. Unless otherwise specified, the carbocycle may be attached at any carbon atom which results in a stable structure and, if substituted, may be substituted at any suitable carbon atom which results in a stable structure. The term comprises cycloalkyl (including spiro cycloalkyl), cycloalkylene, cycloalkenyl, cycloalkenylene, cycloalkynyl, and cycloalkynylene, and the like.

The terms "cycloalkyl" or "cycloalkyl group" mean a stable aliphatic saturated 3- to 15-membered monocyclic or polycyclic monovalent radical consisting solely of carbon and hydrogen atoms which may comprise one or more fused or bridged ring(s), preferably a 5- to 7-membered monocyclic or 7- to 10-membered bicyclic ring. Unless otherwise specified, the cycloalkyl ring may be attached at any carbon atom which results in a stable structure and, if substituted, may be substituted at any suitable carbon atom which results in a stable structure. Exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, norbornanyl, adamantyl, tetrahydronaphthyl (tetralin), 1-decalinyl, bicyclo[2.2.2]octanyl, 1-methylcyclopropyl, 2-methylcyclopentyl, 2-methylcyclooctyl, and the like.

The terms "cycloalkenyl" or "cycloalkenyl group" mean a stable aliphatic 3- to 15-membered monocyclic or polycyclic monovalent radical having at least one carbon-carbon double bond and consisting solely of carbon and hydrogen atoms which may comprise one or more fused or bridged ring(s), preferably a 5- to 7-membered monocyclic or 7- to 10-membered bicyclic ring. Unless otherwise specified, the cycloalkenyl ring may be attached at any carbon atom which results in a stable structure and, if substituted, may be substituted at any suitable carbon atom

which results in a stable structure. Exemplary cycloalkenyl groups include cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclononenyl, cyclodecenyl, norbornenyl, 2-methylcyclopentenyl, 2-methylcyclooctenyl, and the like.

The terms "cycloalkynyl" or "cycloalkynyl group" mean a stable aliphatic 8- to 15-membered monocyclic or polycyclic monovalent radical having at least one carbon-carbon triple bond and consisting solely of carbon and hydrogen atoms which may comprise one or more fused or bridged ring(s), preferably a 8- to 10-membered monocyclic or 12- to 15-membered bicyclic ring. Unless otherwise specified, the cycloalkynyl ring may be attached at any carbon atom which results in a stable structure and, if substituted, may be substituted at any suitable carbon atom which results in a stable structure. Exemplary cycloalkynyl groups include, cyclooctynyl, cyclononynyl, cyclodecynyl, 2-methylcyclooctynyl, and the like.

The terms "cycloalkylene" or "cycloalkylene group" mean a stable saturated aliphatic 3- to 15-membered monocyclic or polycyclic divalent radical consisting solely of carbon and hydrogen atoms which may comprise one or more fused or bridged ring(s), preferably a 5- to 7-membered monocyclic or 7- to 10-membered bicyclic ring. Unless otherwise specified, the cycloalkyl ring may be attached at any carbon atom which results in a stable structure and, if substituted, may be substituted at any suitable carbon atom which results in a stable structure. Exemplary cycloalkylene groups include cyclopentylene, and the like.

The terms "cycloalkenylene" or "cycloalkenylene group" mean a stable aliphatic 5- to 15-membered monocyclic or polycyclic divalent radical having at least one carbon-carbon double bond and consisting solely of carbon and hydrogen atoms which may comprise one or more fused or bridged ring(s), preferably a 5- to 7-membered monocyclic or 7- to 10-membered bicyclic ring. Unless otherwise specified, the cycloalkenylene ring may be attached at any carbon atom which results in a stable structure and, if substituted, may be substituted at any suitable carbon atom which results in a stable structure. Exemplary cycloalkenylene groups include cyclopentenylene, cyclohexenylene, cycloheptenylene, cyclooctenylene, cyclononenylene, cyclodecenylene, norbornenylene, 2-methylcyclopentenylene, 2-methylcyclooctenylene, and the like.

The terms "cycloalkynylene" or "cycloalkynylene group" mean a stable aliphatic 8- to 15-membered monocyclic or polycyclic divalent radical having at least one carbon-carbon triple bond and consisting solely of carbon and hydrogen atoms which may comprise one or more fused or bridged ring(s), preferably a 8- to 10-membered monocyclic or 12- to 15-membered bicyclic ring. Unless otherwise specified, the cycloalkynylene ring may be attached at any carbon atom which results in a stable structure and, if substituted, may be substituted at any suitable carbon atom which results in a stable structure. Exemplary cycloalkynylene groups include cyclooctynylene, cyclononynylene, cyclodecynylene, 2-methylcyclooctynylene, and the like.

The terms "aryl" or "aryl group" mean an aromatic carbocyclic monovalent or divalent radical of from 6 to 14 carbon atoms having a single ring (e.g., phenyl or phenylene) or multiple condensed rings (e.g., naphthyl or anthranyl). Unless otherwise specified, the aryl ring may be attached at any suitable carbon atom which results in a stable structure and, if substituted, may be substituted at any suitable carbon atom which results in a stable structure. Exemplary aryl groups include phenyl, naphthyl, anthryl, phenanthryl, indanyl, indenyl, biphenyl, and the like. It may be abbreviated "Ar".

The terms "heteroaryl" or "heteroaryl group" mean a stable aromatic 5- to 14-membered, monocyclic or polycyclic monovalent or divalent radical which may comprise one or more fused or bridged ring(s), preferably a 5- to 7-membered monocyclic or 7- to 10-membered bicyclic radical, having from one to four heteroatoms in the ring(s) independently selected from nitrogen, oxygen, and sulfur, wherein any sulfur heteroatoms may optionally be oxidized and any nitrogen heteroatom may optionally be oxidized or be quaternized. Unless otherwise specified, the heteroaryl ring may be attached at any suitable heteroatom or carbon atom which results in a stable structure and, if substituted, may be substituted at any suitable heteroatom or carbon atom which results in a stable structure. Exemplary and preferred heteroaryls include furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, indolizinyl, azaindolizinyl, indolyl, azaindolyl, diazaindolyl, dihydroindolyl, dihydroazaindoyl, isoindolyl, azaisoindolyl, benzofuranyl, furanopyridinyl, furanopyrimidinyl, furanopyrazinyl, furanopyridazinyl, dihydrobenzofuranyl, dihydrofuranopyridinyl,

dihydrofuranopyrimidinyl, benzodioxolanyl, benzothienyl, thienopyridinyl, thienopyrimidinyl, thienopyrazinyl, thienopyridazinyl, dihydrobenzothienyl, dihydrothienopyridinyl, dihydrothienopyrimidinyl, indazolyl, azaindazolyl, diazaindazolyl, benzimidazolyl, imidazopyridinyl, benzthiazolyl, thiazolopyridinyl, thiazolopyrimidinyl, benzoxazolyl, oxazolopyridinyl, oxazolopyrimidinyl, benzisoxazolyl, purinyl, chromanyl, azachromanyl, quinolizinyl, quinolinyl, dihydroquinolinyl, tetrahydroquinolinyl, isoquinolinyl, dihydroisoquinolinyl, tetrahydroisoquinolinyl, cinnolinyl, azacinnolinyl, phthalazinyl, azaphthalazinyl, quinazolinyl, azaquinazolinyl, quinoxalinyl, azaquinoxalinyl, naphthyridinyl, dihydronaphthyridinyl, tetrahydronaphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, and phenoxazinyl, and the like.

The terms "heterocycle", "heterocycle group", "heterocyclyl", or "heterocyclyl group" mean a stable non-aromatic 5- to 14-membered monocyclic or polycyclic, monovalent or divalent, ring which may comprise one or more fused or bridged ring(s), preferably a 5- to 7-membered monocyclic or 7- to 10-membered bicyclic ring, having from one to three heteroatoms in the ring(s) independently selected from nitrogen, oxygen, and sulfur, wherein any sulfur heteroatoms may optionally be oxidized and any nitrogen heteroatom may optionally be oxidized or be quaternized. Unless otherwise specified, the heterocyclyl ring may be attached at any suitable heteroatom or carbon atom which results in a stable structure and, if substituted, may be substituted at any suitable heteroatom or carbon atom which results in a stable structure. Exemplary and preferred heterocycles include pyrrolinyl, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrofuranyl, hexahydropyrimidinyl, hexahydropyridazinyl, and the like.

The term "compounds of Formula (I)" and equivalent expressions are mean to embrace either or both of compounds of Formula (IA) and compounds of Formula (IB) as the context permits.

The term "compounds of the invention" and equivalent expressions are meant to embrace compounds of Formula (I) as herein described, including the tautomers, the prodrugs, the salts, particularly the pharmaceutically acceptable salts, and the solvates and hydrates thereof, where the context so permits. In general and preferably, the compounds of the invention and the

formulas designating the compounds of the invention are understood to only include the stable compounds thereof and exclude unstable compounds, even if an unstable compound might be considered to be literally embraced by the compound formula. Similarly, reference to intermediates, whether or not they themselves are claimed, is meant to embrace their salts and solvates, where the context so permits. For the sake of clarity, particular instances when the context so permits are sometimes indicated in the text, but these instances are purely illustrative and it is not intended to exclude other instances when the context so permits.

The terms "optional" or "optionally" mean that the subsequently described event or circumstances may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution.

The terms "stable compound" or "stable structure" mean a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic or diagnostic agent. For example, a compound which would have a "dangling valency" or is a carbanion is not a compound contemplated by the invention.

The term "substituted" means that any one or more hydrogens on an atom of a group or moiety, whether specifically designated or not, is replaced with a selection from the indicated group of substituents, provided that the atom's normal valency is not exceeded and that the substitution results in a stable compound. If a bond to a substituent is shown to cross the bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound, then such substituent may be bonded via any atom in such substituent. For example, when the substituent is piperazinyl, piperidinyl, or tetrazolyl, unless specified otherwise, such piperazinyl, piperidinyl, or tetrazolyl group may be bonded to the rest of the compound of the invention via any atom in such piperazinyl, piperidinyl, or tetrazolyl group. Generally, when any substituent or group occurs more than one time in any constituent or compound, its definition on each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0 to 2 R^5, then such

group is optionally substituted with up to two R^5 groups and R^5 at each occurrence is selected independently from the defined list of possible R^5. Such combinations of substituents and/or variables, however, are permissible only if such combinations result in stable compounds.

In a specific embodiment, the term "about" or "approximately" means within 20%, preferably within 10%, and more preferably within 5% of a given value or range.

The yield of each of the reactions described herein is expressed as a percentage of the theoretical yield.

B. Salt, Prodrug, Derivative, and Solvate Terms and Conventions

The terms "prodrug" or "prodrug derivative" mean a covalently-bonded derivative or carrier of the parent compound or active drug substance which undergoes at least some biotransformation prior to exhibiting its pharmacological effect(s). In general, such prodrugs have metabolically cleavable groups and are rapidly transformed *in vivo* to yield the parent compound, for example, by hydrolysis in blood, and generally include esters and amide analogs of the parent compounds. The prodrug is formulated with the objectives of improved chemical stability, improved patient acceptance and compliance, improved bioavailability, prolonged duration of action, improved organ selectivity, improved formulation (e.g., increased hydrosolubility), and/or decreased side effects (e.g., toxicity). In general, prodrugs themselves have weak or no biological activity and are stable under ordinary conditions. Prodrugs can be readily prepared from the parent compounds using methods known in the art, such as those described in A Textbook of Drug Design and Development, Krogsgaard-Larsen and H. Bundgaard (eds.), Gordon & Breach, 1991, particularly Chapter 5: "Design and Applications of Prodrugs"; Design of Prodrugs, H. Bundgaard (ed.), Elsevier, 1985; Prodrugs: Topical and Ocular Drug Delivery, K.B. Sloan (ed.), Marcel Dekker, 1998; Methods in Enzymology, K. Widder *et al.* (eds.), Vol. 42, Academic Press, 1985, particularly pp. 309-396; Burger's Medicinal Chemistry and Drug Discovery, 5th Ed., M. Wolff (ed.), John Wiley & Sons, 1995, particularly Vol. 1 and pp. 172-178 and pp. 949-982; Pro-Drugs as Novel Delivery Systems, T. Higuchi and V. Stella (eds.), Am. Chem. Soc., 1975; Bioreversible Carriers in Drug Design, E.B. Roche (ed.), Elsevier, 1987, each of which is incorporated herein by reference in their entireties.

The term "pharmaceutically acceptable prodrug" as used herein means a prodrug of a compound of the invention which is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible.

The term "salt" means an ionic form of the parent compound or the product of the reaction between the parent compound with a suitable acid or base to make the acid salt or base salt of the parent compound. Salts of the compounds of the present invention can be synthesized from the parent compounds which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts are prepared by reacting the free base or acid parent compound with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base in a suitable solvent or various combinations of solvents.

The term "pharmaceutically acceptable salt" means a salt of a compound of the invention which is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, generally water or oil-soluble or dispersible, and effective for their intended use. The term includes pharmaceutically-acceptable acid addition salts and pharmaceutically-acceptable base addition salts. As the compounds of the present invention are useful in both free base and salt form, in practice, the use of the salt form amounts to use of the base form. Lists of suitable salts are found in, e.g., S.M. Birge *et al.*, J. Pharm. Sci., 1977, 66, pp. 1-19, which is hereby incorporated by reference in its entirety.

The term "pharmaceutically-acceptable acid addition salt" means those salts which retain the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, nitric acid, phosphoric acid, and the like, and organic acids such as acetic acid, trichloroacetic acid, trifluoroacetic acid, adipic acid, alginic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, 2-acetoxybenzoic acid, butyric acid, camphoric acid, camphorsulfonic acid, cinnamic acid, citric acid, digluconic acid, ethanesulfonic acid, glutamic acid, glycolic acid, glycerophosphoric acid, hemisulfic acid,

heptanoic acid, hexanoic acid, formic acid, fumaric acid, 2-hydroxyethanesulfonic acid (isethionic acid), lactic acid, maleic acid, hydroxymaleic acid, malic acid, malonic acid, mandelic acid, mesitylenesulfonic acid, methanesulfonic acid, naphthalenesulfonic acid, nicotinic acid, 2-naphthalenesulfonic acid, oxalic acid, pamoic acid, pectinic acid, phenylacetic acid, 3-phenylpropionic acid, picric acid, pivalic acid, propionic acid, pyruvic acid, pyruvic acid, salicylic acid, stearic acid, succinic acid, sulfanilic acid, tartaric acid, *p*-toluenesulfonic acid, undecanoic acid, and the like.

The term "pharmaceutically-acceptable base addition salt" means those salts which retain the biological effectiveness and properties of the free acids and which are not biologically or otherwise undesirable, formed with inorganic bases such as ammonia or hydroxide, carbonate, or bicarbonate of ammonium or a metal cation such as sodium, potassium, lithium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like. Particularly preferred are the ammonium, potassium, sodium, calcium, and magnesium salts. Salts derived from pharmaceutically-acceptable organic nontoxic bases include salts of primary, secondary, and tertiary amines, quaternary amine compounds, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion-exchange resins, such as methylamine, dimethylamine, trimethylamine, ethylamine, diethylamine, triethylamine, isopropylamine, tripropylamine, tributylamine, ethanolamine, diethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, *N*-ethylpiperidine, tetramethylammonium compounds, tetraethylammonium compounds, pyridine, *N,N*-dimethylaniline, *N*-methylpiperidine, *N*-methylmorpholine, dicyclohexylamine, dibenzylamine, *N,N*-dibenzylphenethylamine, 1-ephenamine, *N,N'*-dibenzylethylenediamine, polyamine resins, and the like. Particularly preferred organic nontoxic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline, and caffeine.

The term "solvate" means a physical association of a compound with one or more solvent molecules or a complex of variable stoichiometry formed by a solute (for example, a compound of Formula (I)) and a solvent, for example, water, ethanol, or acetic acid. This physical association may involve varying degrees of ionic and covalent bonding, including hydrogen

bonding. In certain instances, the solvate will be capable of isolation, for example, when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. In general, the solvents selected do not interfere with the biological activity of the solute. Solvates encompasses both solution-phase and isolatable solvates. Representative solvates include hydrates, ethanolates, methanolates, and the like.

The term "hydrate" means a solvate wherein the solvent molecule(s) is/are H_2O.

The compounds of the present invention as discussed below include the free base or acid thereof, their salts, solvates, and prodrugs and may include oxidized sulfur atoms or quaternized nitrogen atoms in their structure, although not explicitly stated or shown, particularly the pharmaceutically acceptable forms thereof. Such forms, particularly the pharmaceutically acceptable forms, are intended to be embraced by the appended claims.

C. Isomer Terms and Conventions

The term "isomers" means compounds having the same number and kind of atoms, and hence the same molecular weight, but differing with respect to the arrangement or configuration of the atoms in space. The term includes stereoisomers and geometric isomers.

The terms "stereoisomer" or "optical isomer" mean a stable isomer that has at least one chiral atom or restricted rotation giving rise to perpendicular dissymmetric planes (e.g., certain biphenyls, allenes, and spiro compounds) and can rotate plane-polarized light. Because asymmetric centers and other chemical structure exist in the compounds of the invention which may give rise to stereoisomerism, the invention contemplates stereoisomers and mixtures thereof. The compounds of the invention and their salts include asymmetric carbon atoms and may therefore exist as single stereoisomers, racemates, and as mixtures of enantiomers and diastereomers. Typically, such compounds will be prepared as a racemic mixture. If desired, however, such compounds can be prepared or isolated as pure stereoisomers, i.e., as individual enantiomers or diastereomers, or as stereoisomer-enriched mixtures. As discussed in more detail below, individual stereoisomers of compounds are prepared by synthesis from optically active starting materials containing the desired chiral centers or by preparation of mixtures of enantiomeric products followed by separation or resolution, such as conversion to a mixture of

diastereomers followed by separation or recrystallization, chromatographic techniques, use of chiral resolving agents, or direct separation of the enantiomers on chiral chromatographic columns. Starting compounds of particular stereochemistry are either commercially available or are made by the methods described below and resolved by techniques well-known in the art.

The term "enantiomers" means a pair of stereoisomers that are non-superimposable mirror images of each other.

The terms "diastereoisomers" or "diastereomers" mean optical isomers which are not mirror images of each other.

The terms "racemic mixture" or "racemate" mean a mixture containing equal parts of individual enantiomers.

The term "non-racemic mixture" means a mixture containing unequal parts of individual enantiomers.

The term "geometrical isomer" means a stable isomer which results from restricted freedom of rotation about double bonds (e.g., *cis*-2-butene and *trans*-2-butene) or in a cyclic structure (e.g., *cis*-1,3-dichlorocyclobutane and *trans*-1,3-dichlorocyclobutane). Because carbon-carbon double (olefinic) bonds, C=N double bonds, cyclic structures, and the like may be present in the compounds of the invention, the invention contemplates each of the various stable geometric isomers and mixtures thereof resulting from the arrangement of substituents around these double bonds and in these cyclic structures. The substituents and the isomers are designated using the *cis/trans* convention or using the *E* or *Z* system, wherein the term "*E*" means higher order substituents on opposite sides of the double bond, and the term "*Z*" means higher order substituents on the same side of the double bond. A thorough discussion of *E* and *Z* isomerism is provided in J. March, Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 4th ed., John Wiley & Sons, 1992, which is hereby incorporated by reference in its entirety. Several of the following examples represent single *E* isomers, single *Z* isomers, and mixtures of *E/Z* isomers. Determination of the *E* and *Z* isomers can be done by analytical methods such as x-ray crystallography, ^{1}H NMR, and ^{13}C NMR.

Some of the compounds of the invention can exist in more than one tautomeric form. As mentioned above, the compounds of the invention include all such tautomers.

It is well-known in the art that the biological and pharmacological activity of a compound is sensitive to the stereochemistry of the compound. Thus, for example, enantiomers often exhibit strikingly different biological activity including differences in pharmacokinetic properties, including metabolism, protein binding, and the like, and pharmacological properties, including the type of activity displayed, the degree of activity, toxicity, and the like. Thus, one skilled in the art will appreciate that one enantiomer may be more active or may exhibit beneficial effects when enriched relative to the other enantiomer or when separated from the other enantiomer. Additionally, one skilled in the art would know how to separate, enrich, or selectively prepare the enantiomers of the compounds of the invention from this disclosure and the knowledge of the prior art.

Thus, although the racemic form of drug may be used, it is often less effective than administering an equal amount of enantiomerically pure drug; indeed, in some cases, one enantiomer may be pharmacologically inactive and would merely serve as a simple diluent. For example, although ibuprofen had been previously administered as a racemate, it has been shown that only the *S*-isomer of ibuprofen is effective as an anti-inflammatory agent (in the case of ibuprofen, however, although the *R*-isomer is inactive, it is converted *in vivo* to the *S*-isomer, thus, the rapidity of action of the racemic form of the drug is less than that of the pure *S*-isomer). Furthermore, the pharmacological activities of enantiomers may have distinct biological activity. For example, *S*-penicillamine is a therapeutic agent for chronic arthritis, while *R*-penicillamine is toxic. Indeed, some purified enantiomers have advantages over the racemates, as it has been reported that purified individual isomers have faster transdermal penetration rates compared to the racemic mixture. See U.S. Pat. Nos. 5,114,946 and 4,818,541.

Thus, if one enantiomer is pharmacologically more active, less toxic, or has a preferred disposition in the body than the other enantiomer, it would be therapeutically more beneficial to administer that enantiomer preferentially. In this way, the patient undergoing treatment would

be exposed to a lower total dose of the drug and to a lower dose of an enantiomer that is possibly toxic or an inhibitor of the other enantiomer.

Preparation of pure enantiomers or mixtures of desired enantiomeric excess (ee) or enantiomeric purity are accomplished by one or more of the many methods of (a) separation or resolution of enantiomers, or (b) enantioselective synthesis known to those of skill in the art, or a combination thereof. These resolution methods generally rely on chiral recognition and include, for example, chromatography using chiral stationary phases, enantioselective host-guest complexation, resolution or synthesis using chiral auxiliaries, enantioselective synthesis, enzymatic and nonenzymatic kinetic resolution, or spontaneous enantioselective crystallization. Such methods are disclosed generally in Chiral Separation Techniques: A Practical Approach (2nd Ed.), G. Subramanian (ed.), Wiley-VCH, 2000; T.E. Beesley and R.P.W. Scott, Chiral Chromatography, John Wiley & Sons, 1999; and Satinder Ahuja, Chiral Separations by Chromatography, Am. Chem. Soc., 2000. Furthermore, there are equally well-known methods for the quantitation of enantiomeric excess or purity, for example, GC, HPLC, CE, or NMR, and assignment of absolute configuration and conformation, for example, CD ORD, X-ray crystallography, or NMR.

In general, all tautomeric forms and isomeric forms and mixtures, whether individual geometric isomers or stereoisomers or racemic or non-racemic mixtures, of a chemical structure or compound is intended, unless the specific stereochemistry or isomeric form is specifically indicated in the compound name or structure.

D. Pharmaceutical Administration and Diagnostic and Treatment Terms and Conventions

The term "patient" includes both human and non-human mammals.

The term "effective amount" means an amount of a compound according to the invention which, in the context of which it is administered or used, is sufficient to achieve the desired effect or result. Depending on the context, the term effective amount may include or be synonymous with a pharmaceutically effective amount or a diagnostically effective amount.

The terms "pharmaceutically effective amount" or "therapeutically effective amount" means an amount of a compound according to the invention which, when administered to a patient in need thereof, is sufficient to effect treatment for disease-states, conditions, or disorders for which the compounds have utility. Such an amount would be sufficient to elicit the biological or medical response of a tissue, system, or patient that is sought by a researcher or clinician. The amount of a compound of according to the invention which constitutes a therapeutically effective amount will vary depending on such factors as the compound and its biological activity, the composition used for administration, the time of administration, the route of administration, the rate of excretion of the compound, the duration of treatment, the type of disease-state or disorder being treated and its severity, drugs used in combination with or coincidentally with the compounds of the invention, and the age, body weight, general health, sex, and diet of the patient. Such a therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to their own knowledge, the prior art, and this disclosure.

The term "diagnostically effective amount" means an amount of a compound according to the invention which, when used in a diagnostic method, apparatus, or assay, is sufficient to achieve the desired diagnostic effect or the desired biological activity necessary for the diagnostic method, apparatus, or assay. Such an amount would be sufficient to elicit the biological or medical response in a diagnostic method, apparatus, or assay, which may include a biological or medical response in a patient or in a *in vitro* or *in vivo* tissue or system, that is sought by a researcher or clinician. The amount of a compound according to the invention which constitutes a diagnostically effective amount will vary depending on such factors as the compound and its biological activity, the diagnostic method, apparatus, or assay used, the composition used for administration, the time of administration, the route of administration, the rate of excretion of the compound, the duration of administration, drugs and other compounds used in combination with or coincidentally with the compounds of the invention, and, if a patient is the subject of the diagnostic administration, the age, body weight, general health, sex, and diet of the patient. Such a diagnostically effective amount can be determined routinely by one of ordinary skill in the art having regard to their own knowledge, the prior art, and this disclosure.

The term "modulate" means the ability of a compound to alter the function of the glucocorticoid receptor by, for example, binding to and stimulating or inhibiting the glucocorticoid receptor functional responses.

The term "modulator" in the context of describing compounds according to the invention means a compound that modulates the glucocorticoid receptor function. As such, modulators include, but are not limited to, agonists, partial agonists, antagonists, and partial antagonists.

The term "agonist" in the context of describing compounds according to the invention means a compound that, when bound to the glucocorticoid receptor, enhances or increases the glucocorticoid receptor function. As such, agonists include partial agonists and full agonists.

The term "full agonist" in the context of describing compounds according to the invention means a compound that evokes the maximal stimulatory response from the glucocorticoid receptor, even when there are spare (unoccupied) glucocorticoid receptors present.

The term "partial agonist" in the context of describing compounds according to the invention means a compound that is unable to evoke the maximal stimulatory response from the glucocorticoid receptor, even at concentrations sufficient to saturate the glucocorticoid receptors present.

The term "antagonist" in the context of describing compounds according to the invention means a compound that directly or indirectly inhibits or suppresses the glucocorticoid receptor function. As such, antagonists include partial antagonists and full antagonists.

The term "full antagonist" in the context of describing compounds according to the invention means a compound that evokes the maximal inhibitory response from the glucocorticoid receptor, even when there are spare (unoccupied) glucocorticoid receptors present.

The term "partial antagonist" in the context of describing compounds according to the invention means a compound that is unable to evoke the maximal inhibitory response from the

glucocorticoid receptor, even at concentrations sufficient to saturate the glucocorticoid receptors present.

The terms "treating" or "treatment" mean the treatment of a disease-state in a patient, and include:

(i) preventing the disease-state from occurring in a patient, in particular, when such patient is genetically or otherwise predisposed to the disease-state but has not yet been diagnosed as having it;

(ii) inhibiting or ameliorating the disease-state in a patient, i.e., arresting or slowing its development; or

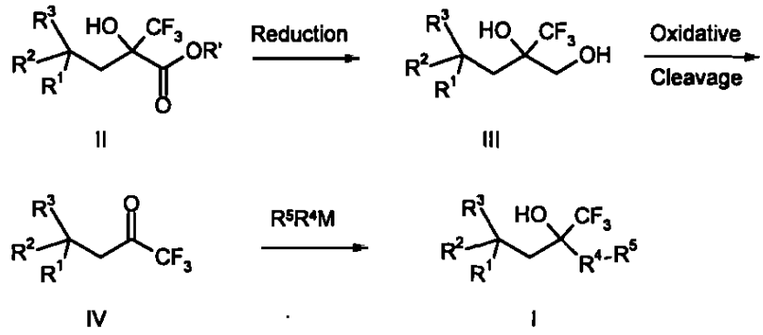
(iii) relieving the disease-state in a patient, i.e., causing regression or cure of the disease-state.

General Synthetic Methods for Making Compounds of Formula (IA) and Formula (IB)

The invention also provides processes for making compounds of Formula (IA) and Formula (IB). In all schemes, unless specified otherwise, R^1 to R^5 in the formulas below shall have the meaning of R^1 to R^5 in the Formula (IA) of the invention described hereinabove; and where appropriate, R^1 to R^6 in the formulas below shall have the meaning of R^1 to R^6 in the Formula (IB) of the invention described hereinabove. Intermediates used in the preparation of compounds of the invention are either commercially available or readily prepared by methods known to those skilled in the art.

Optimum reaction conditions and reaction times may vary depending on the particular reactants used. Unless otherwise specified, solvents, temperatures, pressures, and other reaction conditions may be readily selected by one of ordinary skill in the art. Specific procedures are provided in the Experimental Examples section. Typically, reaction progress may be monitored by thin layer chromatography (TLC), if desired, and intermediates and products may be purified by chromatography on silica gel and/or by recrystallization.

Compounds of Formula (I) may be prepared by the method outlined in Scheme I.

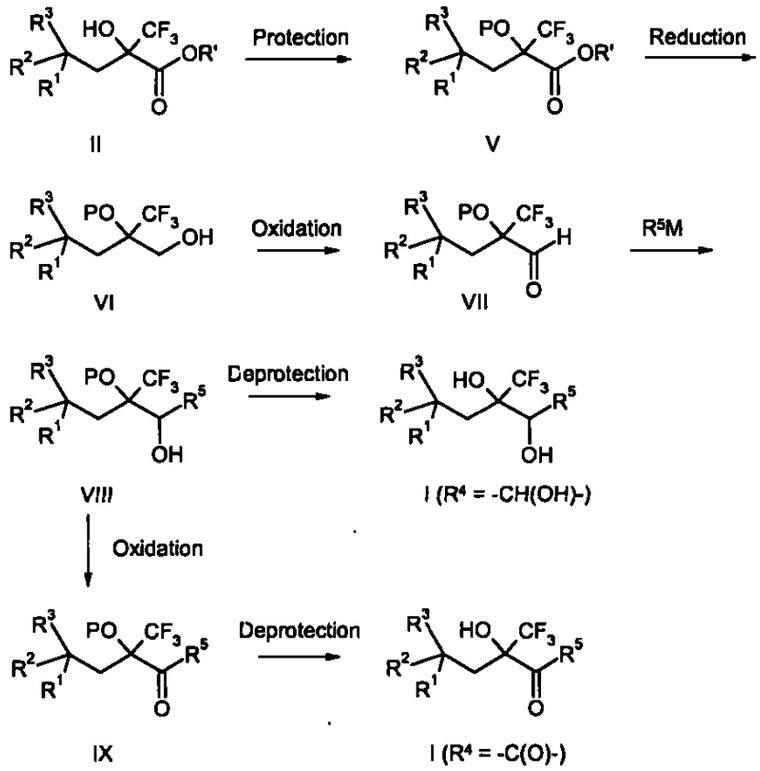


II III IV I

Scheme I

As illustrated in Scheme I, an ester intermediate of Formula (II) where R' is Me or Et, is reduced with a suitable reducing agent, such as lithium aluminum hydride, in a suitable solvent, such as THF or diethyl ether, to produce the 1,2-diol of Formula (III). Oxidative cleavage of 1,2-diols is well-known in the art and may be achieved with periodic acid or lead tetraacetate, for example, in a suitable solvent, such as methanol, to provide the ketone (IV). Reaction of ketone (IV) with a suitable organometallic reagent R^5R^4M, such as a Grignard reagent (M is MgBr or MgCl) or an organolithium reagent (M is Li), in a suitable solvent such as THF or diethyl ether provides the desired compound of Formula (I). Such organolithium reagents and alkylmagnesium halides or Grignard reagents are well-known in the art, for example, Grignard reagents are easily prepared by reacting the corresponding alkyl halide with magnesium metal in a suitable solvent, such as ether or THF, under anhydrous conditions.

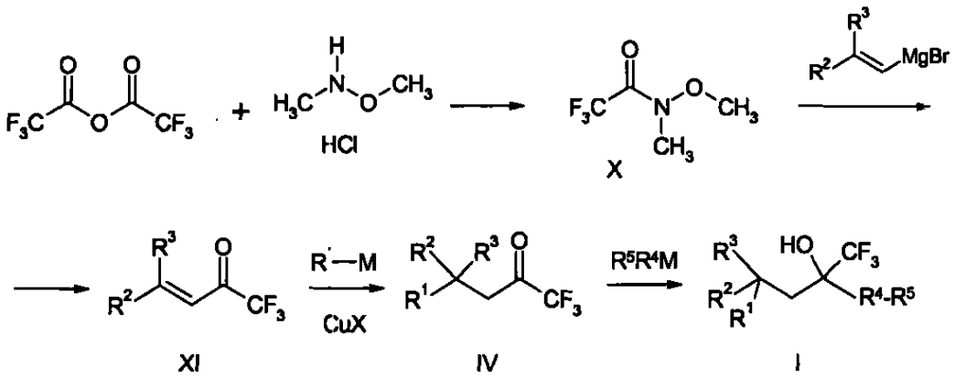
Scheme II outlines another approach that may be used to obtain compounds of Formula (I).



Scheme II

In Scheme II, the hydroxyl function on intermediate (II) is protected to provide ester (V). Hydroxyl protecting groups are well-known in the art, an example of a suitable protecting group is a methoxymethyl ether. Reduction of the ester (V) with a suitable reducing agent such as lithium aluminum hydride provides alcohol (VI). Oxidation of alcohol (VI) with an oxidizing agent such as pyridinium chlorochromate (PCC) provides aldehyde (VII). Treatment of aldehyde (VII) with a suitable organometallic reagent R^5M where M is Li or MgX, and X is Cl, Br, or I, that is, an organolithium reagent or Grignard reagent or alkylmagnesium halide bearing R^5, provides alcohol (VIII). Deprotection by standard methods, which would depend on the protecting group used, gives the desired compound of Formula (I) where R^4 is -CH(OH)-. Oxidation of alcohol (VIII) to (IX) with an oxidizing agent such as PCC or 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one, followed by deprotection provides the desired compound of Formula (I) where R^4 is -C(O)-.

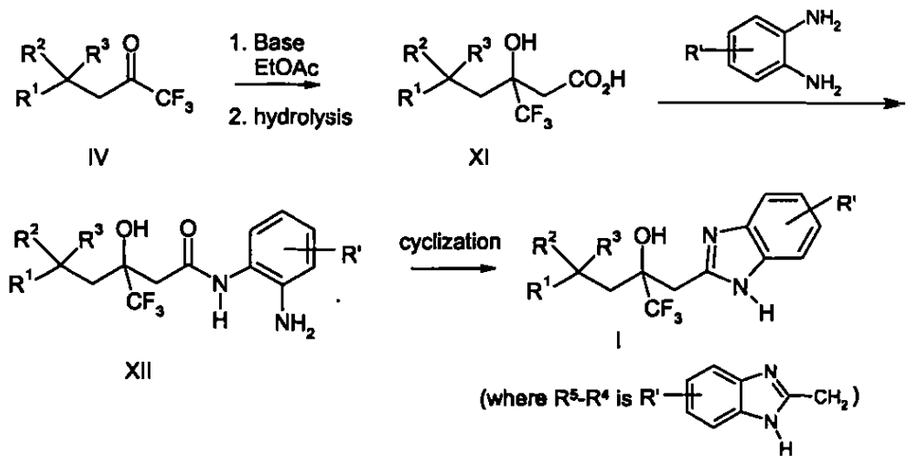
Compounds of Formula (I) may also be prepared by the method outlined in Scheme III.



Scheme III

In this approach, trifluoroacetic anhydride and *N,O*-dimethylhydroxylamine hydrochloride are coupled under basic conditions to afford trifluoroacetamide (X) (Weinreb amide). The Weinreb amide (X) is reacted with a vinyl magnesium bromide bearing R^2 and R^3 to afford the trifluoromethylenone intermediate (XI). The trifluoromethylenone intermediate (XI) is treated with an organocopper reagent, derived from a Grignard or organolithium reagent by treating with a copper salt, to afford the 1,4-addition product (IV). This trifluoro ketone intermediate (IV) is reacted with an organometallic reagent R^4R^5M (as described in Scheme I) to afford the desired compound of Formula (I).

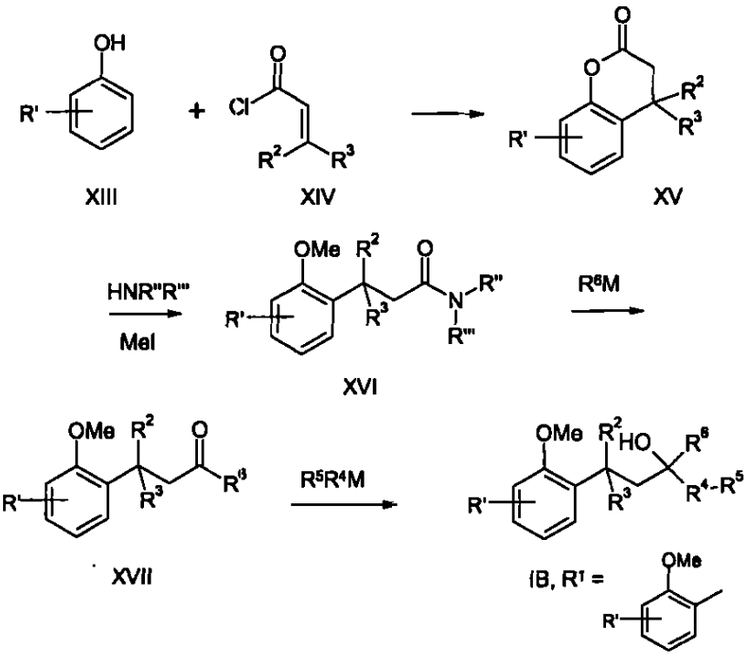
Compounds of Formula (I) in which R^4-R^5 is an optionally substituted benzimidazol-2-ylmethyl group may also be prepared by the procedure outlined in Scheme IV.



Scheme IV

As illustrated in Scheme IV, trifluoromethyl ketone (IV) is reacted with ethyl acetate in the presence of a strong base such as lithium diisopropylamide (LDA) in a suitable solvent such as THF. The intermediate ester is hydrolyzed, for example, by treatment with aqueous base, to provide carboxylic acid intermediate (XII). This carboxylic acid intermediate (XII) is then coupled with an optionally substituted *o*-phenylenediamine under standard coupling conditions known in the art, for example, by treatment with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) in the presence of 1-hydroxybenzotriazole in a suitable solvent such as DMF, to provide compound (XIII). Ring closure by methods known in the art, for example, acid catalyzed ring closure by treatment with polyphosphoric acid, provides the desired compound of Formula (I).

Compounds of Formula (IB) may be prepared by the procedure illustrated in Scheme V.

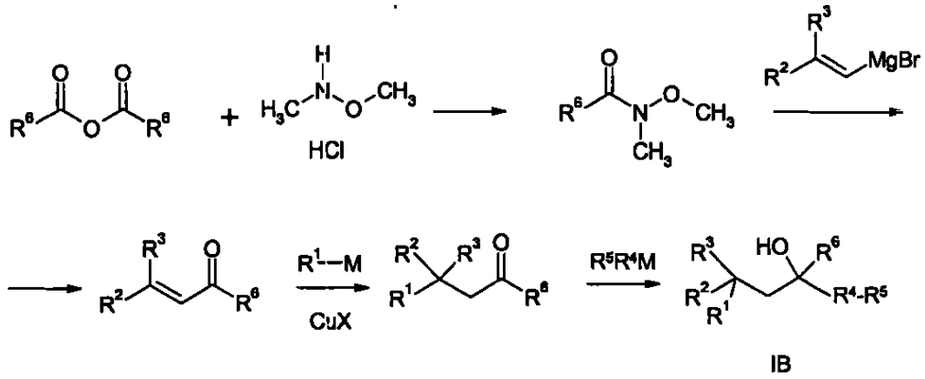


Scheme V

In Scheme V, substituted phenol (XIV) is reacted with an acryloyl chloride bearing R^2 and R^3 (XV) in the presence of a suitable base, such as triethylamine, to provide an intermediate ester which is cyclized by treatment with a Lewis acid, such as aluminum trichloride, in a suitable solvent, such as carbon disulfide, to provide lactone (XVI). The lactone (XVI) is treated with a

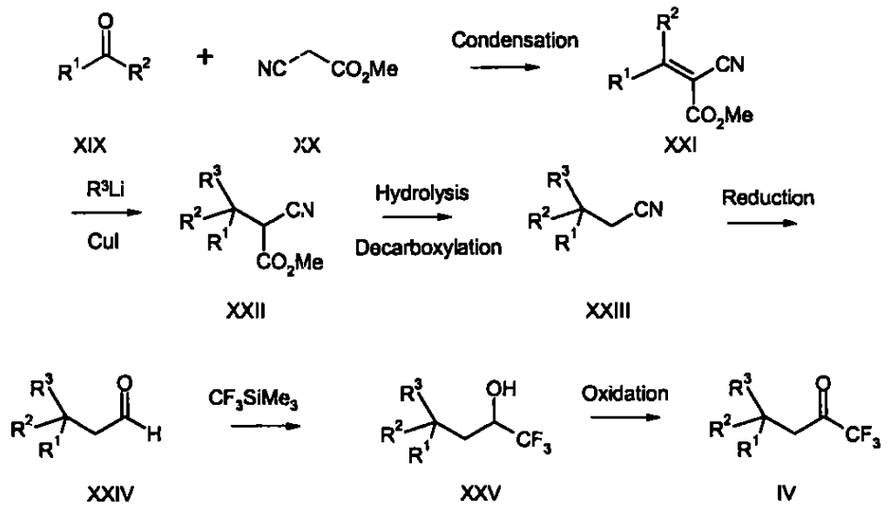
suitable amine HNR''R''', such as morpholine, such that in the resulting amide (XVII), -NR''R''' will function as a leaving group in the subsequent reaction. The intermediate phenol that forms is protected, for example, by reaction with methyl iodide in the presence of a suitable base such as potassium hydroxide to form the protected phenol (XVII), in this case having a methoxy group. The amide is then reacted with an organometallic reagent (R^6M), such as a Grignard reagent (M is MgBr or MgCl) or an organolithium reagent (M is Li), in a suitable solvent, such as THF or diethyl ether, to provide the ketone (XVIII). Reaction of the ketone (XVIII) with R^5R^4M as described in the last step in Scheme I provides the desired compound of Formula (IB) where R^1 is an optionally substituted methoxyphenyl group.

In a more general procedure, suitable for a variety of R^1, one may use a method analogous to that described in Scheme III. As illustrated in Scheme VI, using a Weinreb amide bearing R^6 one may employ the method described in Scheme III to prepare the desired compound of Formula (IB).



Scheme VI

An alternative method to prepare intermediate (IV), used in the methods illustrated in Schemes I-IV, is illustrated in Scheme VII.



Scheme VII

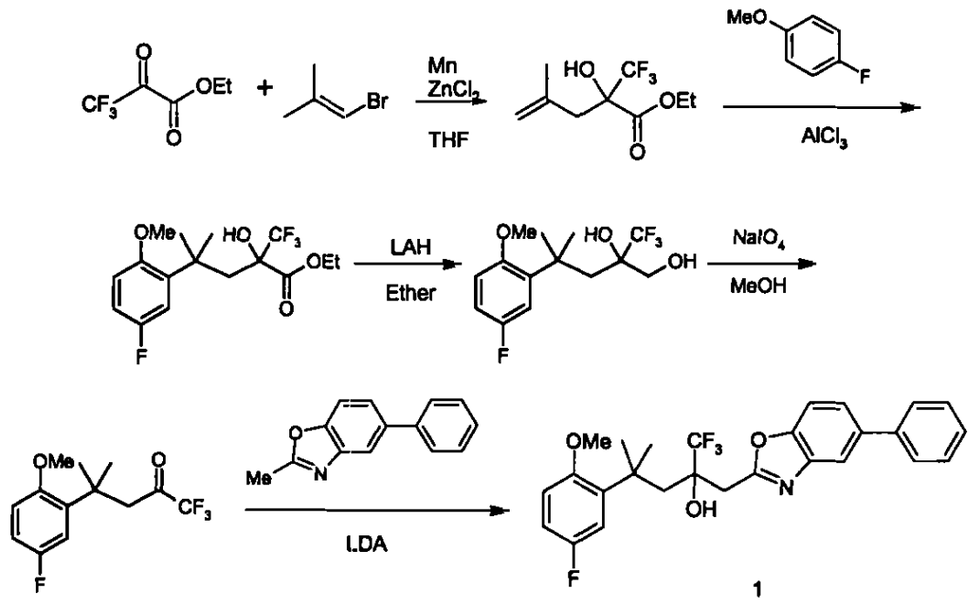
In Scheme VII, a ketone bearing R^1 and R^2 (XIX) is reacted with a cyanoacetic acid ester, such as the methyl ester (XX) under condensation conditions known in the art to provide the olefin (XXI). Reaction of olefin (XXI) with R^3Li in the presence of a copper salt such as CuI provides compound (XXII). Hydrolysis and decarboxylation of compound (XXII) results in nitrile (XXIII). Reduction of nitrile (XXIII), for example, by treatment with diisobutylaluminum hydride (DIBAL), provides aldehyde (XXIV). Treatment of aldehyde (XXIV) with trimethyl(trifluoromethyl)silane in the presence of an ammonium salt such as tetrabutylammonium fluoride provides alcohol (XXV). Oxidation of alcohol (XXV) by methods known in the art, such as by treatment with the Dess-Martin periodinane, provides compound (IV).

In order that this invention be more fully understood, the following examples are set forth. These examples are for the purpose of illustrating embodiments of this invention, and are not to be construed as limiting the scope of the invention in any way since, as recognized by one skilled in the art, particular reagents or conditions could be modified as needed for individual compounds. Starting materials used are either commercially available or easily prepared from commercially available materials by those skilled in the art.

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Experimental Examples

Example 1: Synthesis of 1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(5-phenylbenzoxazol-2-ylmethyl)pentan-2-ol



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To a mixture of 8.5 g (49.9 mmol) of ethyl trifluoromethylpyruvate, 6.6 g (120 mmol) of manganese, and 0.65 g (4.8 mmol) of zinc chloride in 40 mL of THF warmed to reflux was added 200 μL (2 mmol) of 1-bromo-2-methylpropene. After 30 minutes, 9.13 mL (90.5 mmol) of 1-bromo-2-methylpropene in 30 mL of THF was added dropwise over a 1 hour period. The mixture was refluxed for 1 hour after the addition and was then cooled to 0°C and diluted with 150 mL of saturated aqueous ammonium chloride and 100 mL of EtOAc. The organic phase was separated and the aqueous layer extracted with three 100 mL portions of EtOAc. The combined organic layers were washed with two 50 mL portions of saturated aqueous ammonium chloride, followed by two 50 mL portions of brine, dried over magnesium sulfate ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography eluting with EtOAc-hexanes (5:95) to afford 5.9 g (52%) of 2-hydroxy-4-methyl-2-trifluoromethylpent-4-enoic acid ethyl ester.

To a mixture of 5.9 g (26.1 mmol) of the above 2-hydroxy-4-methyl-2-trifluoromethylpent-4-enoic acid ethyl ester in 30 mL of 4-fluoroanisole was added in several portions 5.2 g (39.4 mmol) of aluminum chloride. The mixture became exothermic and turned black with the first

addition and was cooled with an ice-water bath. The mixture was stirred for 3 days and was then poured into 200 mL of ice-cold 1 N aqueous HCl and extracted with three 150 mL portions of EtOAc. The combined organic layers were washed with 50 mL of 1 N aqueous hydrochloric acid, three 50 mL portions of brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography eluting with EtOAc-hexanes (1:9, then 2:8, then 3:7, then 4:6) to afford 6.6 g (71%) of 4-(5-fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentanoic acid ethyl ester.

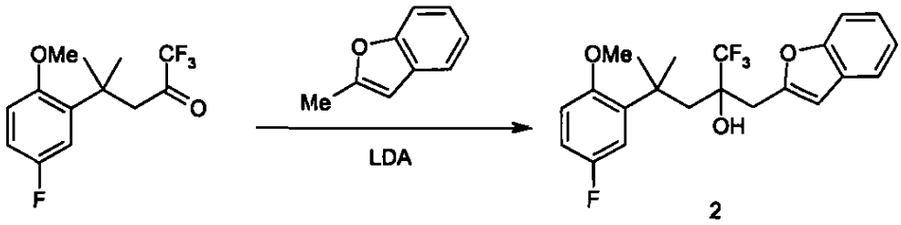
To a chilled solution (ice-water bath) of 6 g (17.0 mmol) of the above 4-(5-fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentanoic acid ethyl ester in 60 mL of dry THF, 2.4 g (61.5 mmol) of lithium aluminum hydride was added in portions. After the addition, the cold bath was removed and the mixture was stirred at room temperature overnight. The mixture was then warmed to reflux for 3 hour and then cautiously quenched by slow addition to 100 mL of THF containing 2 mL of water. Additional water was then cautiously added for a total of 15 mL and the resulting mixture stirred for 2 hours. The excess water was dried over magnesium sulfate and 300 mL of EtOAc was added. After 1 hour, the mixture was filtered through diatomaceous earth and concentrated *in vacuo* to afford 4.9 g (92%) of 4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-trifluoromethylpentane-1,2-diol as an oil.

To a solution of 4.9 g (15.8 mmol) of the above 4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-trifluoromethylpentane-1,2-diol in 100 mL of MeOH was added 10 g (45.9 mmol) of sodium periodate. The mixture was stirred for 4 hours and was then diluted with 100 mL of ether and 100 mL of hexanes, filtered through diatomaceous earth, and concentrated *in vacuo*. The crude residue was dissolved in hexanes and passed through a pad of silica gel eluting first with hexanes then with EtOAc-hexanes (2:98, then 4:96) to afford 3.85 g (87%) of 1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-one as a clear oil.

n-Butyl lithium (0.246 mL, 1.6 M in hexanes) was added to a solution of diisopropyl amine (0.055 mL, 0.45 mmol) in anhydrous THF (5 mL) at 0°C. The reaction mixture was cooled to -78°C and stirred for 15 minutes. 2-Methyl-5-phenyl benzoxazole (75 mg, 0.4 mmol) dissolved in anhydrous THF (2 mL) was added to this mixture dropwise. After the addition, the reaction mixture was stirred for 15 to 30 minutes. 1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-

methylpentan-2-one (100 mg, 0.4 mmol) was added as a solution in anhydrous THF (2 mL) in one portion, the cold bath was removed and the reaction was stirred at room temperature for 12 hours. THF was evaporated under reduced pressure. Water (2 mL) was added to the residue and the mixture was extracted with three 5 mL portions of EtOAc. The extract was dried over magnesium sulfate. After evaporation, the residue was chromatographed on a silica gel column to provide 150 mg of the title compound as white crystals, m.p. 103°C-104°C.

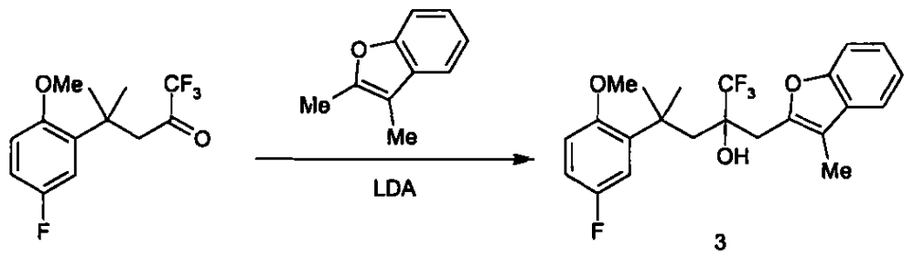
Example 2: Synthesis of 2-benzoxazol-2-ylmethyl-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol



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n-Butyl lithium (0.246 mL, 1.6 M in hexanes) was added to a solution of diisopropyl amine (0.055 mL, 0.45 mmol) in anhydrous THF (5 mL) at 0°C. The reaction mixture was cooled to -78°C and stirred for 15 minutes. A solution of 2-methylbenzofuran (48 mg, 0.4 mmol) in 2 mL anhydrous THF was added dropwise to this mixture. After the addition, the reaction mixture was stirred for 15 to 30 minutes. 1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-one (100 mg, 0.4 mmol) (Example 1) was added as a solution in anhydrous THF (2 mL) in one portion, the cold bath was removed, and the reaction was stirred at room temperature for 12 hours. THF was evaporated under reduced pressure. Water (2 mL) was added to the residue and the mixture was extracted with three 5 mL portions of EtOAc. The extract was dried over magnesium sulfate. After evaporation, the residue was chromatographed on a silica gel column to provide 86 mg of the title compound as an oil.

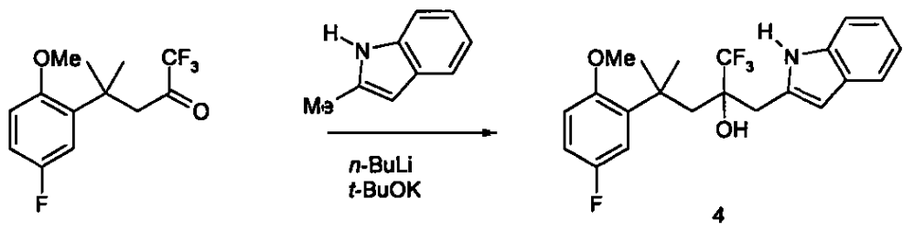
Example 3: Synthesis of 1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(3-methylbenzofuran-2-ylmethyl)pentan-2-ol



3

n-Butyl lithium (0.246 mL, 1.6 M in hexanes) was added to a solution of diisopropyl amine (0.055 mL, 0.45 mmol) in anhydrous THF (5 mL) at 0°C. The reaction mixture was cooled to -78°C and stirred for 15 minutes. A solution of 2,3-dimethylbenzofuran (48 mg, 0.4 mmol) in 2 mL anhydrous THF was added dropwise to this mixture. After the addition, the reaction mixture was stirred for 15 to 30 minutes. 1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-one (100 mg, 0.4 mmol) (Example 1) was added as a solution in anhydrous THF (2 mL) in one portion, the cold bath was removed, and the reaction was stirred at room temperature for 12 hours. THF was evaporated under reduced pressure. Water (2 mL) was added to the residue and the mixture was extracted with three 5 mL portions of EtOAc. The extract was dried over magnesium sulfate. After evaporation, the residue was chromatographed on a silica gel column to provide 80 mg of the title compound as an oil.

Example 4: Synthesis of 1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol

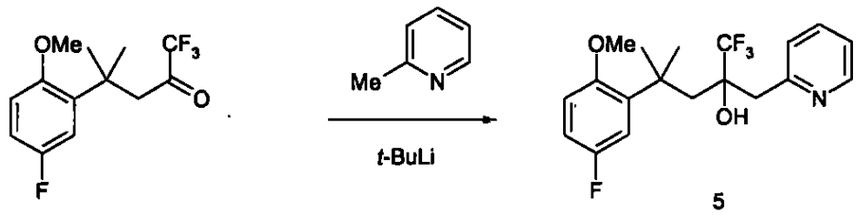


4

n-Butyl lithium (0.673 mL, 1.6 M in hexanes) followed by potassium *tert*-butoxide (81 mg, 0.718 mmol) was added to a stirred solution of 2-methyl indole (47 mg, 0.359 mmol) in anhydrous diethyl ether (5 mL) at room temperature. Within 5 to 10 minutes, the reaction mixture turned bright orange. 1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-one (100 mg, 0.4 mmol) (Example 1) was then added dropwise as a solution in anhydrous diethyl ether (2 mL). The reaction was quenched with water after 1 hour, extracted with three 5 mL portions of EtOAc, dried over magnesium sulfate, and concentrated under reduced

pressure. The residue was purified by column chromatography on silica gel affording 45 mg of the title compound as an oil.

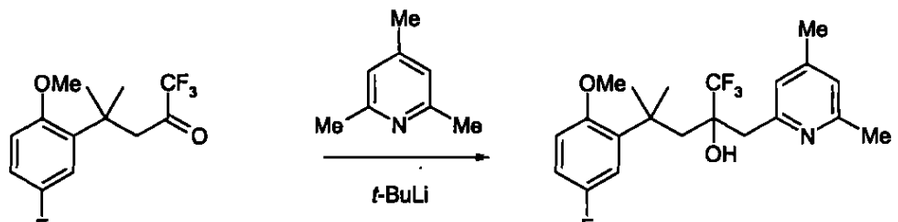
Example 5: Synthesis of 1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(pyridin-2-ylmethyl)-4-methylpentan-2-ol



5

tert-Butyl lithium (1.7 M in pentane, 0.5 mL) was added dropwise to a solution of 2-methylpyridine (0.050 g) in THF (0.5 mL) cooled to -70°C under argon. The mixture was stirred at -70°C for 10 minutes and 1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-one (0.080 g) (Example 1) in THF (0.5 mL) was added over 1 minute. The reaction mixture was stirred for 5 minutes and then quenched with MeOH. The reaction mixture was concentrated *in vacuo* and the residue fractionated directly by preparative layer chromatography on silica gel (methylene chloride-hexanes (1:1)) to give the 57 mg of the title compound, m.p. 94°C-96°C.

Example 6: Synthesis of 1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(4,6-dimethylpyridin-2-ylmethyl)-4-methylpentan-2-ol

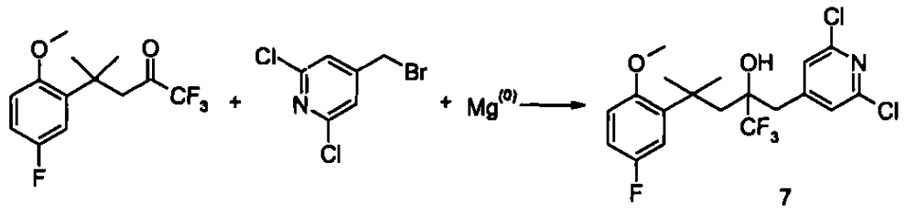


6

tert-Butyl lithium (1.7 M in pentane, 0.5 mL) was added dropwise to a solution of 2,4,6-trimethylpyridine (0.12 g) in THF (0.5 mL) cooled to -70°C under argon. The mixture was stirred at -70°C for 15 minutes and 1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-one (0.10 g) (Example 1) in THF (0.5 mL) was added. The reaction mixture was stirred for 20 minutes and then quenched with acetic acid. The mixture was diluted with

EtOAc, washed with water, dried, filtered, and concentrated *in vacuo*. Fractionation by preparative layer chromatography on silica gel (methylene chloride-hexanes) followed by crystallization gave 43 mg of the title compound, m.p. 95°C-98°C.

Example 7: Synthesis of 2-(2,6-dichloropyridin-4-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol

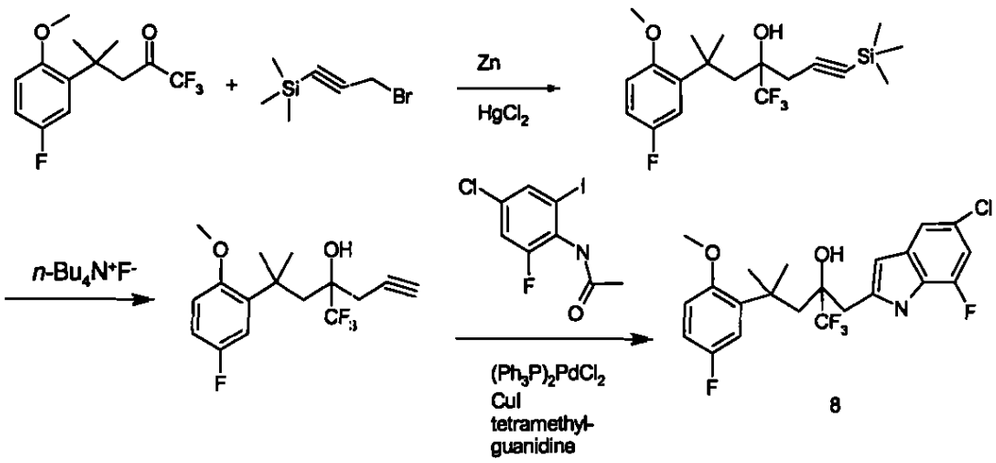


7

To a 100 mL dry round bottom flask was added 73 mg (3.0 mmol) of magnesium powder, a couple of I_2 crystals, and 5 mL of dry diethyl ether, and the mixture was allowed to stir under argon. 4-Bromomethyl-2,6-dichloropyridine (723 mg, 3.0 mmol) in 10 mL of diethyl ether was added dropwise through a dropping funnel and the resulting mixture was heated to reflux for 1 hour. 1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-one (278 mg, 1.0 mmol) (Example 1) in diethyl ether (5 mL) was carefully added dropwise through a dropping funnel and the mixture was allowed to stir to reflux temperature for 4 hours and then overnight (16 hours) at room temperature. The reaction was quenched with the addition of 3 mL of aqueous NH_4Cl solution, and the resulting mixture was extracted with three 30 mL portions of EtOAc, washed with H_2O (10 mL) and brine (10 mL), and the organic phase was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using an EtOAc-hexanes gradient. Combined product fractions were concentrated *in vacuo* to afford the desired product which was further purified by preparative-HPLC using a gradient of 80%-100% (CH_3CN-water) in 15 minutes and a flow rate of 20 mL/min to afford 76 mg of the title compound (17.2% yield) as a yellowish liquid.

Example 8: Synthesis of 2-(5-chloro-7-fluoro-1*H*-indol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol

137

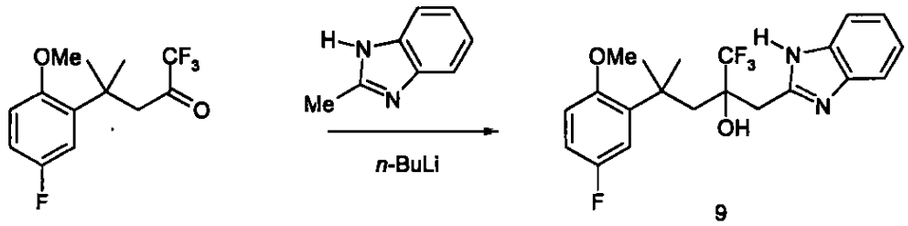


A stirred suspension of zinc dust (0.656 g) and mercuric chloride (25 mg) in 5 mL of anhydrous THF was cooled on ice. A solution of trimethylsilyl-propargyl bromide (0.96 g, 5 mmol) in anhydrous THF (1 mL) was added, the ice-bath was removed, and the reaction mixture was stirred at room temperature for 20 hours. To solution of the resulting organozinc reagent was added a solution of 1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-one (0.2 g, 0.72 mmol) (Example 1) in anhydrous THF (1 mL) and the reaction mixture was stirred at room temperature for 4 hours. TLC (hexanes-EtOAc (95:5)) indicated consumption of starting material with a single more polar spot. The reaction mixture was quenched with a saturated solution of ammonium chloride. The resulting mixture was extracted with three 30 mL portions of dichloromethane, the combined extracts were washed with two 20 mL portions of water, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude product was purified by column chromatography over silica gel eluting with hexanes-EtOAc (95:5) to give the desired alcohol intermediate as a colorless oil.

To a stirred solution of the above alcohol (200 mg, 0.51 mmol) in anhydrous THF (2 mL) cooled in ice was added 0.5 mL of 1 M solution of tetrabutylammonium fluoride solution in THF. After 30 minutes, TLC in hexanes-EtOAc (95:5) indicated consumption of starting material. The reaction mixture was quenched with a saturated solution of ammonium chloride (5 mL), extracted with ether (100 mL), washed with two 25 mL portions of water, dried over anhydrous sodium sulfate, and concentrated *in vacuo*, providing the desired terminal acetylene intermediate (160 mg, 98%).

A mixture of the above acetylene intermediate (85 mg, 0.27 mmol), 4-chloro-2-fluoro-6-iodoacetanilide (90 mg, 0.29 mmol), bis(triphenylphosphine)palladium(II) chloride catalyst (20 mg, 0.028 mmol), copper (I) iodide (8 mg, 0.042 mmol), and tetramethylguanidine (0.2 mL) in anhydrous dioxane (0.5 mL) was stirred and heated in an oil-bath maintained at 80°C for 20 hours. After cooling to room temperature, the reaction mixture was diluted with dichloromethane (25 mL) and filtered through diatomaceous earth, which was then rinsed with dichloromethane. The filtrate and the washings were collected, washed with three 20 mL portions of 1 N H_2SO_4, three 20 mL portions of water, dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give a brownish oil. The crude product was purified by preparative TLC eluting with hexanes-EtOAc (90:10). The band corresponding to R_f 0.26 was collected, providing the title compound as an oil.

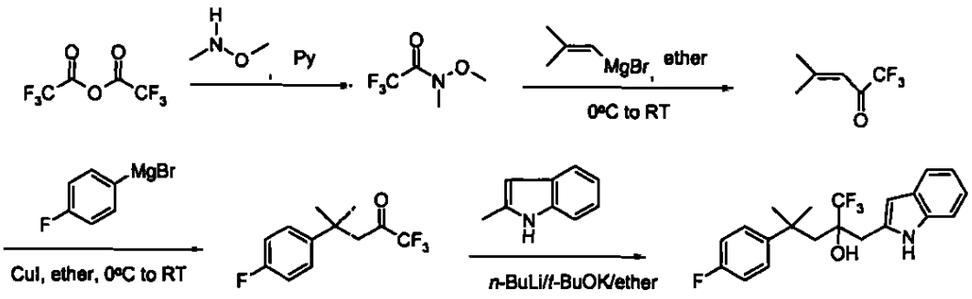
Example 9: Synthesis of 2-(1*H*-benzimidazol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol



9

To a solution of 2-methylbenzimidazole (300 mg, 2.3 mmol) in 20 mL of anhydrous THF at -30°C, *n*-butyl lithium (1.6 M in pentanes, 3 mL, 4.8 mmol) was slowly added. The resulting red-colored heterogeneous mixture was stirred for 2 hours at this temperature, then a solution of 1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-one (700 mg, 2.55 mmol) (see Example 1) in anhydrous THF (1 mL) was added dropwise. The reaction temperature was allowed to slowly warm to room temperature over a period of 2 hours, at which time reaction was treated with saturated NH_4Cl solution. The resulting mixture was extracted with diethyl ether. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford an oil which was purified by chromatography on silica gel to provide 200 mg of unchanged 2-methylbenzimidazole and 60 mg of the title compound as a white solid, m.p. 80°C-82°C.

Example 10: Synthesis of 2-(1*H*-indol-2-ylmethyl)-1,1,1-trifluoro-4-(4-fluorophenyl)-4-methylpentan-2-ol



10

To a mixture of 15.8 g of *N,O*-dimethylhydroxylamine hydrochloride in 400 mL of CH_2Cl_2, 21.7 mL of trifluoroacetic anhydride was added dropwise at 0°C. Pyridine (37 mL) was then added to the above mixture dropwise at 0°C. The resulting mixture was allowed to stir at 0°C for 30 minutes, and was then quenched with water. The organic layer was washed with water, 1 N aqueous HCl, water and brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was pumped under vacuum for 5 minutes providing 2,2,2-trifluoro-*N*-methoxy-*N*-methylacetamide as a colorless oil.

A mixture of 3 g of 2,2,2-trifluoro-*N*-methoxy-*N*-methylacetamide and 30 mL of anhydrous ether was cooled down to 0°C and treated with 42 mL of a 0.5 M solution of 2-methyl propenylmagnesium bromide in THF. The reaction was stirred at 0°C for 0.5 minutes and then warmed to room temperature and stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl and extracted with ether three times. The organic layers were combined and washed with water and brine, dried over magnesium sulfate, and filtered. The resulting ether/THF solution of 1,1,1-trifluoro-4-methylpent-3-en-2-one was used for the next reaction without further purification.

To a 2 M ether/THF solution of 1,1,1-trifluoro-4-methylpent-3-en-2-one was added 3.8 g of copper (I) iodide and 10 mL of a 2 M ether solution of 4-fluorophenylmagnesium bromide at 0°C. The mixture was warmed to room temperature and stirred for 2 hours. The reaction was quenched with saturated aqueous NH_4Cl, and extracted three times with EtOAc. The combined organic layers were washed with water, brine, dried over magnesium sulfate, filtered, and

concentrated *in vacuo*. The residue was purified by flash chromatography to yield 460 mg of 1,1,1-trifluoro-4-(4-fluorophenyl)-4-methylpentan-2-one.

To a diethyl ether solution of 53 mg of 2-methylindole was added 3 equivalents of *n*-butyl lithium followed by 90 mg of potassium *tert*-butoxide (*t*-BuOK) (solid) at room temperature. The mixture was allowed to stir for 30 minutes. 1,1,1-Trifluoro-4-(4-fluorophenyl)-4-methylpentan-2-one (100 mg) in diethyl ether was then added to the above mixture. The reaction was stirred at room for 1 hour. The reaction was quenched with saturated aqueous ammonium chloride, and extracted three times with EtOAc. The combined organic layers were washed with water, brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography to yield 40 mg of the title compound as a foam. Resolution to the (+)- and (-) enantiomers was accomplished by chiral HPLC on a CHIRALCEL® OD™ column, eluting with 10% isopropanol-hexanes.

The following compounds were made by procedures analogous to those described in Example 10.

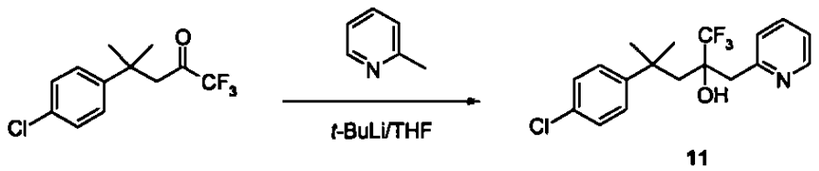
1,1,1-Trifluoro-4-(3-fluorophenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

4-(3,4-Dichlorophenyl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol; and

4-(3,4-Difluorophenyl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol.

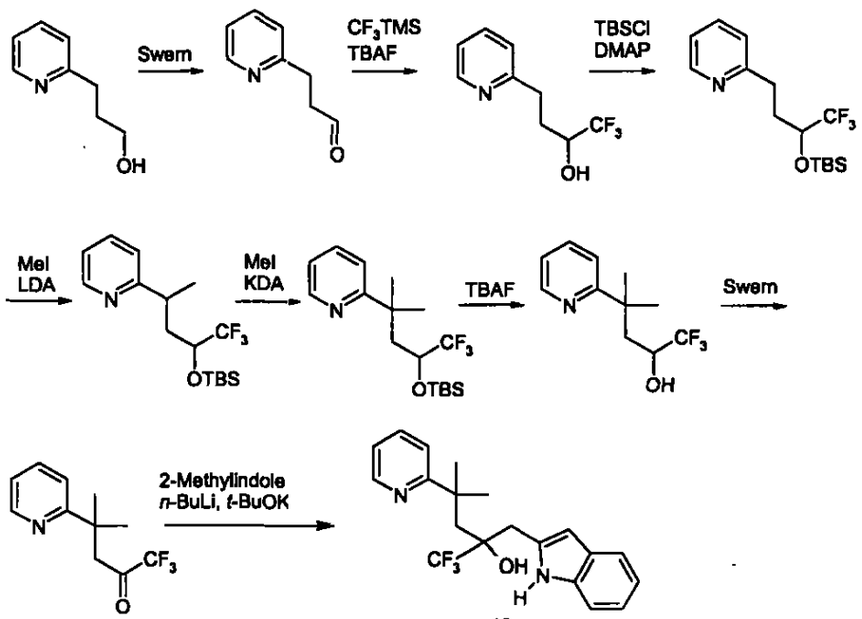
Example 11: Synthesis of 4-(4-chlorophenyl)-1,1,1-trifluoro-4-methyl-2-pyridin-2-ylmethylpentan-2-ol



11

A mixture of 2-picoline in 1 mL of THF was cooled down to -78°C. *tert*-Butyl lithium (1.7 M in pentanes, 0.2 mL (0.34 mmol)) was added dropwise over 5 minutes. The mixture stirred at -78°C for 15 minutes, and then a solution of 40 mg of 4-(4-chlorophenyl)-1,1,1-trifluoro-4-methylpentan-2-one in 0.5 mL of THF was added. Stirring continued at -78°C for 20 minutes. The reaction was quenched with 0.5 N HCl and extracted three times with EtOAc. The organic layers were combined and washed with water, brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography to yield 9.6 mg of the title compound as a light yellowish oil.

Example 12: Synthesis of 1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-pyridin-2-ylpentan-2-ol



12

A solution of 4.5 mL (9 mmol, 1.2 eq.) of oxalyl chloride (2.0 M solution in dichloromethane) was diluted with 15 mL of dichloromethane. To this solution was added a solution of 1.2 mL

(17.5 mmol, 2.4 eq.) of DMSO in 3 mL of dichloromethane at -60°C and the mixture was stirred for 10 minutes at this temperature. To this mixture was added a solution of 1 g (7.3 mmol) of 4-pyridinepropanol in 7 mL of dichloromethane at -60°C. The resulting mixture was stirred at -60°C for 15 minutes, then 5.0 mL (36.5 mmol, 5.0 eq.) of triethylamine was added at this temperature. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature and was quenched with water. The organic layer was separated and the aqueous layer was extracted three times with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography providing 3-pyridin-2-ylpropionaldehyde as a brown oil. Yield: 769 mg (78%).

A solution of 760 mg (5.6 mmol) of 3-pyridin-2-ylpropionaldehyde in 3 mL of THF was treated with 13.6 mL (6.8 mmol, 1.2 eq.) of trimethyl(trifluoromethyl)silane (0.5 M solution in THF) and 0.06 mL (0.06 mmol) of tetrabutylammonium fluoride (1.0 M solution in THF) at 0°C. The resulting mixture was stirred at 0°C for 10 minutes, and quenched with 1 N HCl solution. After stirring for 5 minutes, the pH of the reaction mixture was adjusted to 9 with saturated $NaHCO_3$ solution, and the product was extracted into ether. The ethereal layer was washed with water and brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography to give 706 mg (61%) of 1,1,1-trifluoro-4-pyridin-2-ylbutan-2-ol as a colorless oil.

A solution of 700 mg (3.4 mmol) of 1,1,1-trifluoro-4-pyridin-2-ylbutan-2-ol in 10 mL of dichloromethane was treated with 616 mg (4.1 mmol, 1.2 eq.) of *tert*-butyldimethylsilyl chloride, 697 mg (10.2 mmol, 3.0 eq.) of imidazole and 415 ng (3.4 mmol) of 4-dimethylaminopyridine at 0°C. The resulting mixture was allowed to warm to room temperature and was stirred for 36 hours. Then the mixture was concentrated and the residue was purified by flash chromatography to give 970 mg (89%) of 2-[3-(*tert*-butyldimethylsilanyloxy)-4,4,4-trifluorobutyl]pyridine as a colorless oil.

A solution of 810 mg (2.54 mmol) of 2-[3-(*tert*-butyldimethylsilanyloxy)-4,4,4-trifluorobutyl]pyridine in 8 mL of THF was treated with 2.54 mL (3.81 mmol, 1.5 eq.) of LDA (1.5 M solution in cyclohexane) at -75°C. After stirring at -75°C for 45 minutes, 474 µL (7.61

mmol, 3.0 eq.) of methyl iodide was added at -75°C. The resulting mixture was stirred at this temperature for 10 minutes and quenched with saturated NH_4Cl solution. The product was extracted into ether. The ethereal layer was washed with water, brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 750 mg (89%) of 2-[3-(*tert*-butyldimethylsilanyloxy)-4,4,4-trifluoro-1-methylbutyl]pyridine (a mixture of two diastereomers) as a brown oil.

To a solution of 3.87 mL (3.87 mmol, 1.5 eq.) of potassium *tert*-butoxide (1.0 M solution in THF) and 542 µL (3.87 mmol, 1.5 eq.) of diisopropylamine, 1.55 mL (3.87 mmol, 1.5 eq) of *n*-butyl lithium (2.5 M solution in hexanes) was added dropwise at -75°C. The resulting mixture was allowed to warm to -50°C over 15 minutes. Then the reaction mixture was treated with 860 mg (2.58 mmol) of 2-[3-(*tert*-butyldimethylsilanyloxy)-4,4,4-trifluoro-1-methylbutyl]pyridine at -50°C and the resulting mixture was stirred for 30 minutes at -50°C. The reaction mixture was cooled to -75°C and treated with 482 µL (7.74 mmol) of methyl iodide and stirred for 1 minute. The reaction mixture was quenched with saturated NH_4Cl solution and the product was extracted into ether. The ethereal layer was washed with water and brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography to give 555 mg (62%) of 2-[3-(*tert*-butyldimethylsilanyloxy)-4,4,4-trifluoro-1,1-dimethylbutyl]pyridine as a colorless oil.

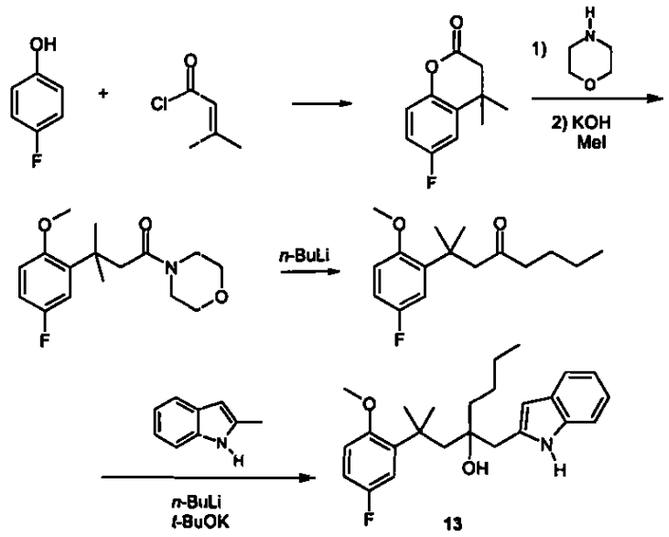
A mixture of 550 mg (1.58 mmol) of 2-[3-(*tert*-butyldimethylsilanyloxy)-4,4,4-trifluoro-1,1-dimethylbutyl]pyridine in 4.5 mL (4.5 mmol) of tetrabutylammonium fluoride (1.0 M solution in THF) was stirred at room temperature for 2 hours. The mixture was concentrated *in vacuo* and the residue was purified by flash chromatography to give 367 mg (99%) of 1,1,1-trifluoro-4-methyl-4-pyridin-2-ylpentan-2-ol as a light yellow oil.

A solution of 516 µL (1.03 mmol, 1.2 eq) of oxalyl chloride (2.0 M solution in dichloromethane) was diluted with 2 mL of dichloromethane. To this solution was added a solution of 146 µL (2.06 mmol, 2.4 eq.) of DMSO in 0.2 mL of dichloromethane at -60°C and the mixture was stirred for 10 minutes at this temperature. Then to this mixture was added a solution of 200 mg (0.86 mmol) of 1,1,1-trifluoro-4-methyl-4-pyridin-2-ylpentan-2-ol in 2 mL of dichloromethane at -60°C. The resulting mixture was stirred at -60°C for 15 minutes and

then 600 µL (4.3 mmol, 5.0 eq.) of triethylamine was added. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature and quenched with water. The organic layer was separated. The aqueous layer was extracted three times with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography, providing 172 mg (86%) 1,1,1-trifluoro-4-methyl-4-pyridin-2-ylpentan-2-one as a brown oil.

To a solution of 42.4 mg (0.324 mmol, 1.5 eq.) of 2-methylindole in 2 mL of THF, 389 µL (0.972 mmol, 4.5 eq.) of *n*-butyl lithium (2.5 M solution in hexanes) and 648 µL (0.648 mmol, 3.0 eq.) of potassium *tert*-butoxide (1.0 M solution in THF) were added dropwise at -75°C. The resulting mixture was allowed to warm to -20°C over 30 minutes. The reaction mixture was cooled to -75°C and a solution of 50 mg (0.216 mmol) of 1,1,1-trifluoro-4-methyl-4-pyridin-2-ylpentan-2-one in 1 mL of THF was added at this temperature. The resulting mixture was stirred at this temperature for 30 minutes and then quenched with saturated NH_4Cl solution. The product was extracted into ether and the ethereal layer was washed with water and brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography to give 22 mg (28%) of the title compound as a white foam.

Example 13: Synthesis of 7-(5-fluoro-2-methoxyphenyl)-5-(indol-2-ylmethyl)-7-methyloctan-5-ol



To a solution of 4-fluorophenol (11.2 g) and dimethylacryloyl chloride (11.9 g) in diethyl ether (200 mL) cooled on ice, triethylamine (14 mL) was added dropwise over 20 minutes. After an additional 30 minutes the reaction mixture was filtered through diatomaceous earth to remove precipitated triethylamine hydrochloride. The ether solution was washed with water and brine, dried over sodium sulfate and evaporated to give crude intermediate ester (19 g). The ester was dissolved in carbon disulfide (50 mL) and aluminum trichloride (19 g) was added slowly as a solid over 1 hour (exothermic reaction). The mixture was then allowed to stir at room temperature overnight. The carbon disulfide was removed in a stream of nitrogen. The residue was quenched by pouring onto ice and neutralized with aqueous sodium bicarbonate. The mixture was extracted with ether, and the organic phase was dried, filtered and evaporated. Chromatography of the residue over a column of silica gel topped with FLORISIL® activated magnesium silicate packing (eluent: ether-hexanes (95:5)) gave the desired lactone as an oil that solidified on trituration with a little hexanes (yield: 10.5 g).

The lactone and morpholine were heated at 80°C (bath temperature) for 30 minutes. Crystalline product appeared. The mixture was cooled to room temperature and triturated with water. The crystalline product was collected by filtration. The product was taken up in DMSO (20 mL) and methyl iodide (2 mL) was added. A solution of potassium hydroxide (1.2 g) in water (10 mL) was added over 20 minutes (moderate exotherm). Additional methyl iodide was added (0.5 mL) followed by potassium hydroxide (0.25 g) in water (5 mL). The mixture was stirred for 20 minutes. The crystalline product was collected by filtration, washed with water and dried under vacuum at 40°C to give 3-(5-fluoro-2-methoxyphenyl)-3-methyl-1-morpholin-4-ylbutan-1-one (5.1 g).

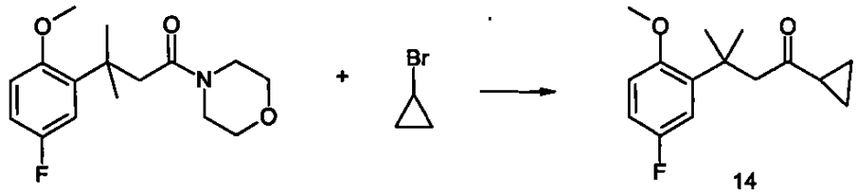
To a solution of the above 3-(5-fluoro-2-methoxyphenyl)-3-methyl-1-morpholin-4-ylbutan-1-one (0.29 g) in THF (2 mL) cooled to -70°C under argon was added dropwise over 5 minutes *n*-butyl lithium (2 M in pentane, 1 mL). The mixture was stirred at -70°C for 15 minutes and then quenched with EtOH (0.2 mL). Water (1 mL) and EtOAc (2 mL) were added and the mixture was warmed to room temperature. The organic phase was separated and washed with water, dried over sodium sulfate, filtered, and evaporated to give the product as an oil (0.26 g).

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To a solution of 2-methylindole (0.13 g) in THF (1 mL) cooled to -70°C under argon was added *n*-butyl lithium (2.5 M in hexane, 1.3 mL) dropwise. After 5 minutes, potassium *tert*-butoxide (1M in THF, 2 mL) was added and the cooling bath was removed. After about 5 minutes, a solid precipitate appeared and the mixture was re-cooled on a dry ice/acetone bath. The ketone from above (0.24 g) in THF (1 mL) was added all at once and the mixture was stirred warming to room temperature over 1 hour. The reaction was quenched with EtOH (0.3 mL) and diluted with EtOAc. The mixture was washed with water, dried, filtered and evaporated. Preparative layer chromatography of the residue (developer methylene chloride) followed by a second preparative layer chromatography (developer: EtOAc-hexanes (5:95)) gave the title compound as an oil (24 mg).

Examples 14-17 illustrate the synthesis of other ketones that may be used as intermediates to prepare compounds of Formula (IB) in methods analogous to those described in Example 13.

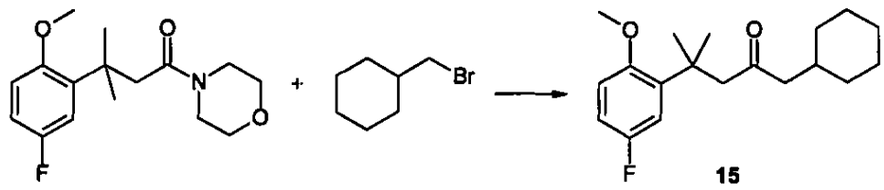
Example 14: Synthesis of 1-cyclopropyl-3-(5-fluoro-2-methoxyphenyl)-3-methylbutan-1-one



14

To a solution of cyclopropyl bromide (0.120 g) in THF (0.8 mL) cooled to -70°C, a solution of *tert*-butyl lithium (1.7 M in pentane, 0.8 mL) was added dropwise over 5 minutes. The mixture was stirred at -70°C for 30 minutes. A solution of 3-(5-fluoro-2-methoxyphenyl)-3-methyl-1-morpholin-4-ylbutan-1-one (0.29 g) in THF (1 mL) was then added all at once and the mixture was stirred for 30 minutes. The mixture was quenched with EtOH (0.3 mL) and warmed to room temperature. The mixture was diluted with EtOAc, washed with water, dried over sodium sulfate, filtered, and evaporated to give the title compound as an oil (0.23 g).

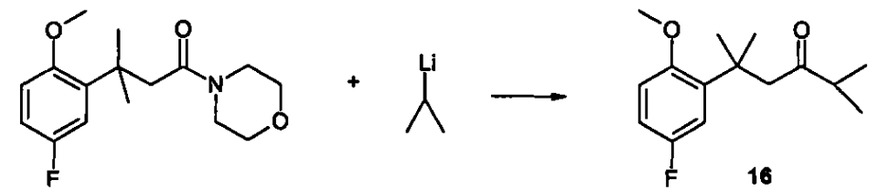
Example 15: Synthesis of 1-cyclohexyl-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-one



15

To a solution of cyclohexylmethyl bromide (0.26 g) in THF (1 mL) cooled to -70°C under argon, *tert*-butyl lithium (1.7 M in pentane, 1.8 mL) was added dropwise over 5 minutes. The mixture was stirred at -70°C for 30 minutes. A solution of 3-(5-fluoro-2-methoxyphenyl)-3-methyl-1-morpholin-4-ylbutan-1-one (0.33 g) in THF (1 mL) was added all at once and the mixture was stirred for one hour. The reaction temperature rose to approximately coming to -20°C. The reaction was quenched with EtOH (0.3 mL), and warmed to room temperature. The mixture was diluted with EtOAc, washed with water, dried, filtered, and evaporated. Chromatography of the residue over silica gel (eluent: hexanes-methylene chloride gradient) gave the title compound as an oil (0.2 g).

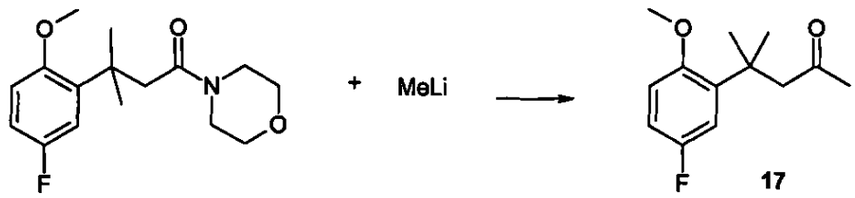
Example 16: Synthesis of 5-(5-fluoro-2-methoxyphenyl)-2,5-dimethylhexan-3-one



16

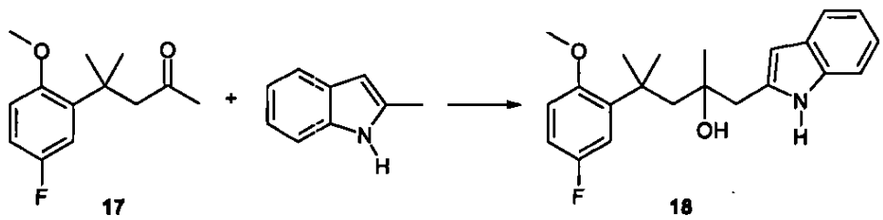
To a solution of 3-(5-fluoro-2-methoxyphenyl)-3-methyl-1-morpholin-4-ylbutan-1-one (0.45 g) in THF (2 mL) stirred under argon and cooled on dry ice/acetone was added isopropyl lithium (0.7M in pentane, 3 mL) over 10 minutes. The mixture was stirred for 20 minutes and quenched with EtOH (0.3 mL). The mixture was warmed to room temperature and water 1 mL was added. The organic phase was separated, washed, dried, filtered, and evaporated. The residue was fractionated over a short column of silica gel (eluent: hexanes-methylene chloride (1:1)) to give the product as an oil (0.40 g).

Example 17: Synthesis of 4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-one



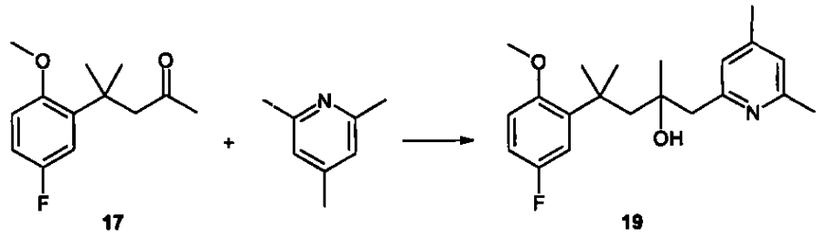
To a solution of 3-(5-fluoro-2-methoxyphenyl)-3-methyl-1-morpholin-4-ylbutan-1-one (0.59 g) in THF (1 mL) stirred under argon and cooled on dry ice/acetone was added methyl lithium (1.4 M in pentane, 2 mL) over 2 minutes. The mixture was stirred for 30 minutes and quenched with EtOH (0.3 mL). The mixture was warmed to room temperature and 1 mL of water was added. The organic phase was separated, washed, dried, filtered, and evaporated. The residue was fractionated over a short column of silica gel (eluent: hexanes-methylene chloride (1:1)) to give the title compound as an oil (0.36 g).

Example 18: Synthesis of 4-(5-fluoro-2-methoxyphenyl)-2-(indol-2-ylmethyl)-4-methylpentan-2-ol



To a solution of 2-methylindole (130 mg) in THF (2 mL) stirred under argon cooled on dry ice/acetone was added *n*-butyl lithium (2M in pentane, 1.6 mL). After 2 minutes, potassium *tert*-butoxide (1M in THF, 2 mL) was added and the mixture was allowed to warm to approximately -20°C. After 5 minutes, precipitate was noted and the mixture was cooled to -70°C. 4-(5-Fluoro-2-methoxyphenyl)-4-methylpentan-2-one (Example 17) (440 mg) in THF (1.5 mL) was added all at once. The cooling bath was removed and the mixture was stirred for 10 minutes and then quenched with EtOH (0.5 mL). The mixture was diluted with EtOAc, washed with water, dried, filtered, and evaporated. Chromatography over silica gel (EtOAc-hexanes (1:9)) gave product which solidified on trituration with hexanes-ether. The solid was recrystallized from ether-hexanes, collected by filtration and dried under vacuum to give 0.11 g of the title compound, m.p. 118°C-120°C.

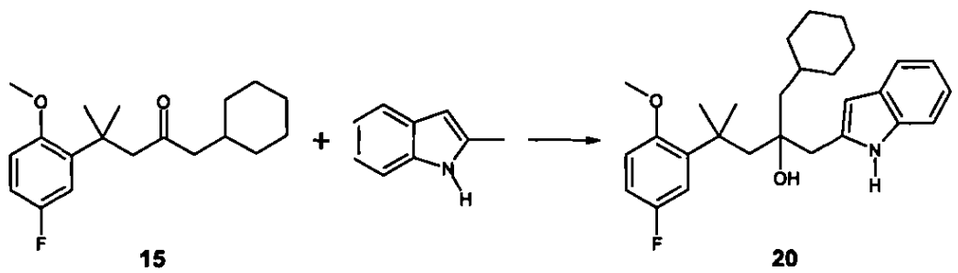
Example 19: Synthesis of 4-(5-fluoro-2-methoxyphenyl)-2-(4,6-dimethylpyridin-2-ylmethyl)-4-methylpentan-2-ol



17 19

To a solution of 2,4,6-trimethylpyridine (0.14 g) in THF (1 mL) stirred under argon and cooled to -70°C, *tert*-butyl lithium (1.7M in pentane, 0.75 mL) was added dropwise over 2 minutes. After stirring for an additional 2 minutes, 4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-one (Example 17) (0.22 g) in THF (0.3 mL) was added all at once. After 5 minutes, the reaction was quenched with EtOH (0.2 mL) and allowed to warm to room temperature. The mixture was diluted with EtOAc, washed with water, dried, filtered, and evaporated. Chromatography of the residue over silica gel (eluent: EtOAc-methylene chloride (2:98 to 8:92 gradient)) gave the product as an oil (0.19 g).

Example 20: Synthesis of 1-cyclohexyl-4-(5-fluoro-2-methoxyphenyl)-2-(indol-2-ylmethyl)-4-methylpentan-2-ol

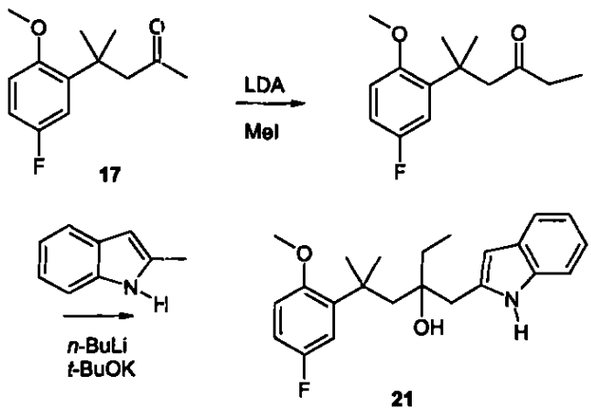


15 20

To a solution of the 2-methylindole (65 mg) in THF (1 mL) stirred under argon cooled on dry ice/acetone was added *n*-butyl lithium (2 M in pentane, 0.8 mL). After 2 minutes, potassium *tert*-butoxide (1M in THF, 1 mL) was added and the mixture was allowed to warm to approximately -20°C. After 5 minutes, a precipitate was noted and the mixture was cooled to -70°C. 1-Cyclohexyl-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-one (Example 15) (100 mg) in THF (1 mL) was added dropwise and the mixture was stirred for 20 minutes at -70°C. The reaction was quenched with EtOH (0.5 mL). The mixture was diluted with EtOAc, washed

with water, dried, filtered, and evaporated. Chromatography over silica gel (methylene chloride-hexanes (1:2)) gave the title compound as an oil (0.095 g).

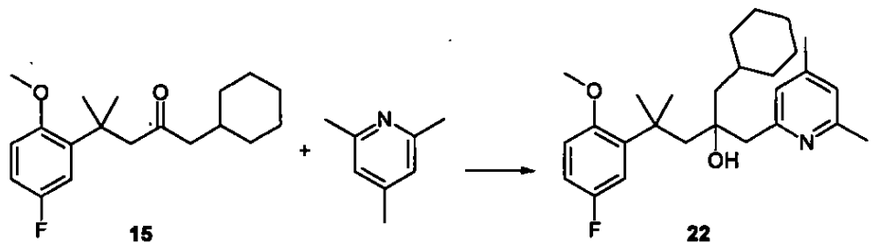
Example 21: Synthesis of 5-(5-fluoro-2-methoxyphenyl)-3-(indol-2-ylmethyl)-5-methylhexan-3-ol



To a solution of lithium diisopropylamide (2 M in THF-hexanes-ethylbenzene, 1.0 mL) in THF 1 mL under argon cooled to -70°C was added dropwise a solution of 4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-one (0.44 g) in THF (1 mL). The mixture was stirred for 30 minutes and then a solution of methyl iodide (0.28 g) in THF (0.5 mL) was added dropwise and the mixture was stirred coming to room temperature overnight. The mixture was diluted with hexanes, washed with water, dried, filtered, and evaporated. Chromatography of the residue over silica gel (hexanes-methylene chloride (gradient 1:4-1:1)) gave the desired hexan-3-one as an oil (0.20 g).

To a solution of 2-methylindole (64 mg) in THF (1 mL) stirred under argon cooled on dry ice / acetone was added *n*-butyl lithium (2M in pentane, 0.8 mL). After 2 minutes, potassium *tert*-butoxide (1M in THF, 1 mL) was added and the mixture was allowed to warm to approximately -20°C. After approximately 5 minutes, a precipitate was noted and the mixture was cooled to -70°C. The hexan-3-one (100 mg) in THF (1 mL) was added dropwise and the mixture was stirred for 20 minutes at -70°C. The reaction was quenched with EtOH (0.5 mL). The mixture was diluted with EtOAc, washed with water, dried, filtered, and evaporated. Chromatography over silica gel (methylene chloride-hexanes (1:2)) gave the title compound as an oil (0.062 g).

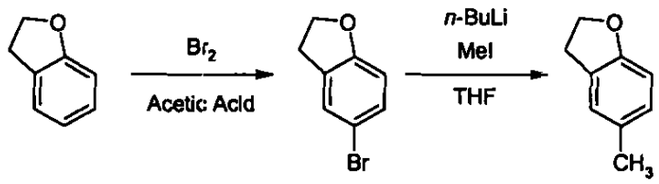
Example 22: Synthesis of 1-cyclohexyl-2-(4,6-dimethylpyridin-2-ylmethyl)- 4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol



To a solution of collidine (0.113 g) in THF (1 mL) cooled to -70°C was added dropwise over 3 minutes *tert*-butyl lithium (1.7 M in pentane, 0.55 mL). The mixture was stirred for 5 minutes and then 1-cyclohexyl-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-one (Example 15) (0.095 g) in THF (0.5 mL) was added dropwise. After 10 minutes at -70°C, the reaction was quenched by addition of EtOH (0.2 mL) and warmed to room temperature. The mixture was diluted with EtOAc, washed with water, dried over sodium sulfate, filtered, and evaporated. The residue was fractionated by preparative layer chromatography (developer: methylene chloride-EtOAc (99:1)) followed by preparative layer chromatography (developer: hexanes-methylene chloride-EtOH (1:1:0.01)) to give the title compound as an oil (73 mg).

Examples 23 and 24 illustrate the synthesis of substituted dihydrobenzofurans. These may be converted to trifluoromethyl ketone intermediates by the procedure described in Example 1 for 4-fluoroanisole.

Example 23: Synthesis of 5-methyl-2,3-dihydrobenzofuran



23

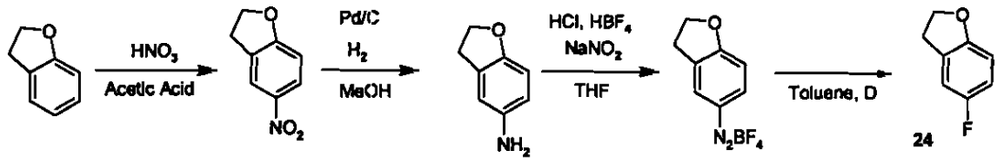
To a chilled (10°C) solution of 10 g (83 mmol) of 2,3-dihydrobenzofuran in 50 mL of acetic acid, 4 mL (78 mmol) of bromine in 6 mL of acetic acid was added dropwise over a 10 minute period. After 1 hour, the mixture was made basic by cautiously pouring the reaction mixture into saturated/solid aqueous sodium bicarbonate solution and stirring overnight. The mixture

was then extracted with three 100 mL portions of EtOAc. The combined organic layers were washed with two 50 mL portions of saturated aqueous sodium bicarbonate, three 50 mL portions of brine, dried over magnesium sulfate, filtered, and concentrated to afford a yellow oil. The oil was diluted with hexanes and passed through a pad of silica gel in a 600 mL funnel eluting with hexanes to afford a white solid which was diluted with cold (dry ice-acetone) hexanes and collected by filtration to afford 4.7 g (28%) of 5-bromo-2,3-dihydrobenzofuran as a white solid, mp 45°C-48°C. The filtrate was concentrated to afford 5.1 g of 5-bromo-2,3-dihydrobenzofuran which was 70% pure.

To a chilled (-78°C) solution of 5.2 g (26.12 mmol) of 5-bromo-2,3-dihydrobenzofuran in anhydrous THF was added 13.4 mL (26.8 mmol) of a 2.0 M solution of *n*-butyl lithium in pentane. After 10 minutes, 4 mL (64.25 mmol) of iodomethane was added dropwise. After the addition, the cold bath was removed and the mixture stirred at room temperature. After 2 hours, the mixture was diluted with 40 mL of saturated aqueous ammonium chloride and extracted with three 30 mL portions of EtOAc. The combined organic layers were washed with three 30 mL portions of brine, dried over magnesium sulfate, filtered, and concentrated to afford 3.7 g of a yellow oil. The oil was distilled under vacuum (Kugelrohr) at 70°C-80°C to afford 1.6 g (45%) of the title compound which was used without further purification.

Using the procedure described in Example 1, the following ketone was prepared: 1,1,1-Trifluoro-4-methyl-4-(5-methyl-2,3-dihydrobenzofuran-7-yl)pentan-2-one.

Example 24: Synthesis of 5-Fluoro-2,3-dihydrobenzofuran



24

To a solution of 25.5 g (0.212 mol) of 2,3-dihydrobenzofuran in 175 mL of acetic acid was added about one quarter of 4.5 mL (0.227 mol) of 70% aqueous nitric acid dropwise. The reaction was monitored by TLC (EtOAc-hexanes, 15:85). The mixture was warmed to 70°C where the reaction began. The remainder of the nitric acid was then added while maintaining the reaction at 70°C. After 30 minutes, the reaction was cooled and poured into 1.5 L of ice

water. The black solid was collected by filtration washing with water. The solid was partitioned between 500 mL of saturated aqueous sodium bicarbonate and 150 mL of EtOAc. The aqueous layer was separated and extracted with three 150 mL portions of EtOAc. The combined organic layers were washed with three 100 mL portions of saturated aqueous sodium bicarbonate, 100 mL of saturated aqueous ammonium chloride, 100 mL of brine, dried over magnesium sulfate, filtered, and concentrated to afford a red oil/solid. The mixture was dissolved in dichloromethane and passed through a pad of silica gel, eluting with dichloromethane, and concentrated. The resulting red mixture was triturated with ether-hexanes (1:1) and filtered to afford 10.5 g (29%) of 5-nitro-2,3-dihydrobenzofuran as a tan solid.

To a suspension of 10.3 g (62.37 mmol) of 5-nitro-2,3-dihydrobenzofuran in 50 mL of MeOH and 10 mL of dichloromethane was added 350 mg of 10% palladium on carbon and the mixture was placed under 55 psi of hydrogen gas. Hydrogen gas uptake was evident during the first 30 minutes. After 18 hours, the mixture was then filtered through diatomaceous earth and concentrated to afford 8.2 g of 2,3-dihydrobenzofuran-5-ylamine as a gray solid which was used without further purification.

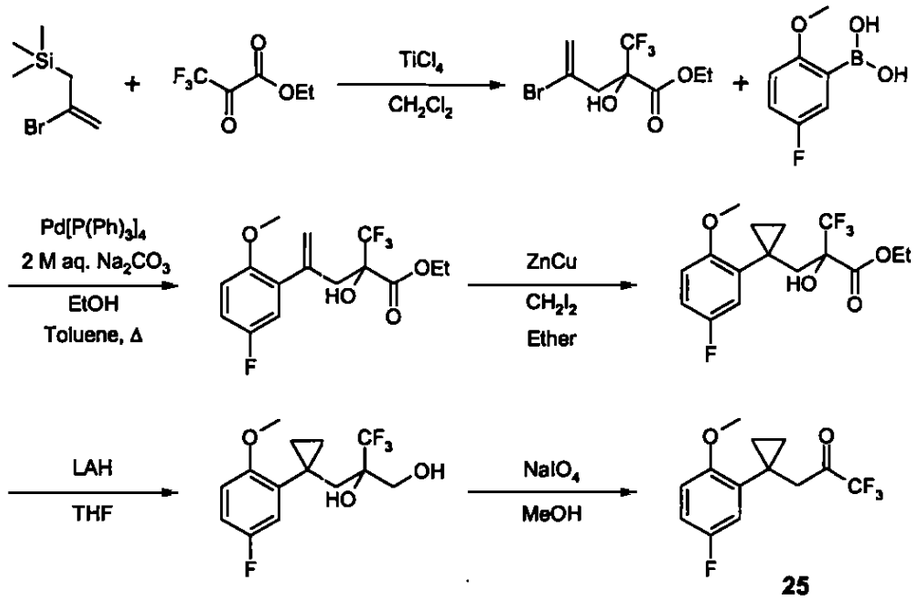
To a solution of 8.2 g (60.66 mmol) of 2,3-dihydrobenzofuran-5-ylamine in 250 mL of THF was added 6 mL of concentrated aqueous HCl in several portions. To the resulting white precipitate was added 11 mL of tetrafluoroboric acid dropwise. The mixture was then chilled (-15°C) and 4.7 g (68.12 mmol) of sodium nitrite in 20 mL of water was added dropwise. The suspension turned deep gray, became homogenous and then a precipitate formed. The mixture was stirred for 30 minutes at -15°C and then the solid was collected by filtration washing with cold water, cold ethanol, and cold ether. The solid was dried by pulling vacuum through the filter cake to afford 9.7 g (68%) of 5-diazonium-2,3-dihydrobenzofuran tetrafluoroborate salt which was used without further purification.

A suspension of 9.7 g (41.46 mmol) of the above diazonium tetrafluoroborate salt in xylenes was warmed at reflux for 1 hour. The mixture was then cooled and diluted with 200 mL of saturated aqueous sodium bicarbonate. The aqueous was separated and extracted with three 50 mL portions of EtOAc. The combined organic layers were washed with 50 mL of aqueous

sodium bicarbonate, 50 mL of brine, dried over magnesium sulfate, filtered, and concentrated to afford an oil. The crude oil was chromatographed on silica gel using EtOAc-hexanes (0:100, then 0.5:99.5) to afford 2.6 g (45%) of the title compound.

Using the procedure described in Example 1, the following ketone was prepared: 1,1,1-Trifluoro-4-(5-fluoro-2,3-dihydrobenzofuran-7-yl)-4-methylpentan-2-one.

Example 25: Synthesis of 1,1,1-trifluoro-3-[1-(5-fluoro-2-methoxyphenyl)cyclopropyl]propan-2-one



25

To a chilled (-78°C) solution of 5.2 mL (30.18 mmol) of 2-bromoallyltrimethylsilane and 5.3 g (31.16 mmol) of ethyl trifluoropyruvate in 75 mL of dichloromethane was added 30 mL (30 mmol) of a 1 M solution of titanium tetrachloride in dichloromethane over a 10 minute period. The cold bath was then removed and the mixture was warmed to room temperature. After 3 hours, the mixture was cautiously added to 100 mL of saturated aqueous ammonium chloride and filtered through diatomaceous earth, washing with dichloromethane. The dichloromethane was separated and the aqueous layer was extracted with three 50 mL portions of dichloromethane. The combined organic layers were washed with two 50 mL portions of saturated aqueous sodium bicarbonate, 50 mL of brine, dried over magnesium sulfate, filtered,

and concentrated to afford 6.7 g (76%) of 4-bromo-2-hydroxy-2-trifluoromethylpent-4-enoic acid ethyl ester as a yellow oil which was used without further purification.

A mixture of 500 mg (1.71 mmol) of 4-bromo-2-hydroxy-2-trifluoromethylpent-4-enoic acid ethyl ester, 509 mg (3 mmol) of 3-fluoro-5-methoxyphenylboronic acid and 25 mg (0.022 mmol) of tetrakis(triphenylphosphine)palladium(0) in 4 mL of toluene, 2 mL of ethanol, and 1 mL of 2 M aqueous sodium carbonate was warmed at reflux. After 24 hours, the mixture was cooled and diluted with saturated aqueous ammonium chloride and extracted with three 10 mL portions of EtOAc. The combined organic layers were washed with three 5 mL portions of brine, dried over magnesium sulfate, filtered, and concentrated. The crude solidified upon standing and was adsorbed onto silica gel and chromatographed on silica gel using EtOAc-hexanes (0:100, then 0.5:99.5, then 1:99, then 2:98) to afford partially purified product. Trituration with ether-hexanes removed an insoluble by product. The filtrate was chromatographed on silica gel using dichloromethane-hexanes (5:95, then 1:9, then 15:85, then 2:8, then 3:7, then 4:6) to afford 280 mg (48%) of 4-(5-fluoro-2-methoxyphenyl)-2-hydroxy-2-trifluoromethylpent-4-enoic acid ethyl ester as an oil which solidified upon standing.

To a solution of 620 mg (1.84 mmol) of 4-(5-fluoro-2-methoxyphenyl)-2-hydroxy-2-trifluoromethylpent-4-enoic acid ethyl ester, 475 mg zinc copper couple, and an iodine crystal in anhydrous ether in a sealed tube warmed to 55°C was added dropwise 500 μL (6.20 mmol) of diiodomethane. The reaction was monitored by TLC in dichloromethane-hexanes (1:1) or ether-hexanes (2:8). After 18 hours, the mixture was cooled, diluted with EtOAc, and filtered through diatomaceous earth. The filtrate was washed with three 10 mL portions of 1 N aqueous HCl, 10 mL of brine, three 10 mL portions of saturated aqueous sodium bicarbonate, dried over magnesium sulfate, filtered, and concentrated. The crude material was adsorbed onto silica gel and chromatographed on silica gel using ether-hexanes (0:100, then 1:99, then 2:98) to afford 494 mg (76%) of 3,3,3-trifluoro-2-[1-(5-fluoro-2-methoxyphenyl)cyclopropylmethyl]-2-hydroxypropionic acid ethyl ester.

To a chilled (0°C) solution of 400 mg (1.14 mmol) of 3,3,3-trifluoro-2-[1-(5-fluoro-2-methoxyphenyl)cyclopropylmethyl]-2-hydroxypropionic acid ethyl ester in 5 mL of anhydrous THF was added 98 mg (2.58 mmol) of lithium aluminum hydride in several portions. The cold

bath was then removed and the mixture was stirred at room temperature. After 4.5 hours, the mixture was cooled in an ice water bath and cautiously quenched with water, dried over magnesium sulfate, and filtered through diatomaceous earth, washing with EtOAc to afford 278 mg (78%) of title compound which was used without further purification. The filter cake was partitioned between 15 mL of 1 N aqueous hydrochloric acid and extracted with three 10 mL portions of EtOAc. The combined organic layers were washed with two 10 mL portions of 1 N aqueous hydrochloric acid, 10 mL of brine, and two 10 mL portions of saturated aqueous sodium bicarbonate, dried over magnesium sulfate, filtered, and concentrated to afford an addition 32 mg (8.9%) of 3,3,3-trifluoro-2-[1-(5-fluoro-2-methoxyphenyl)cyclopropylmethyl]propane-1,2-diol.

To a solution of 310 mg (1.01 mmol) of 3,3,3-trifluoro-2-[1-(5-fluoro-2-methoxyphenyl)cyclopropylmethyl]propane-1,2-diol in 15 mL of MeOH was added 1.5 g (7.01 mmol) of sodium periodate. After 7 hours, the mixture was concentrated and the residue diluted with hexanes and filtered through diatomaceous earth. The crude residue was chromatographed on silica gel using hexanes to load the sample and then eluting with EtOAc-hexanes (0:100, then 0.25:99.75, then 0.5:99.5, then 1:99) to afford 200 mg of the title compound as a clear oil.

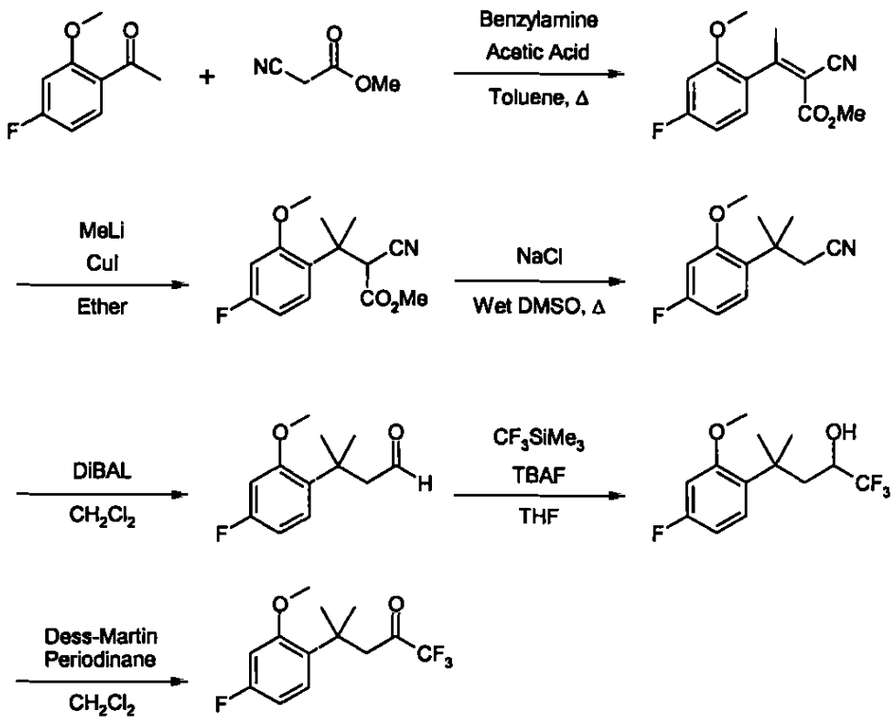
The following trifluoromethyl ketones were also prepared by the method of Example 25:

1,1,1-Trifluoro-3-[1-(2-trifluoromethoxyphenyl)cyclopropyl]propan-2-one;

3-[1-(2,5-Difluorophenyl)cyclopropyl]-1,1,1-trifluoropropan-2-one; and

1,1,1-Trifluoro-3-[1-(4-fluorophenyl)cyclopropyl]propan-2-one.

Example 26: Synthesis of 1,1,1-trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methylpentan-2-one



26

To a round bottom flask fitted with a Dean-Stark trap was added a mixture of 19.54 g (116 mmol) of 4-fluoro-2-methoxyacetophenone, 15.29 mL (174 mmol) of methyl cyanoacetate, 1.42 mL (13 mmol) of benzylamine, and 6.6 mL of acetic acid in 170 mL of toluene and the mixture was warmed to reflux. The reaction was monitored by TLC (EtOAc-hexanes, 2:8). After 18 hours, the reaction was then cooled and concentrated *in vacuo* to afford a dark, orange oil. The crude oil was distilled at 130°C under vacuum (Kugelrohr) to remove unreacted 4-fluoro-2-methoxyactophenone. The crude product was then passed through a pad of silica gel using a 10% EtOAc in a 1:1 mixture of dichloromethane in hexanes to afford 27.64 g (95%) of 2-cyano-3-(4-fluoro-2-methoxyphenyl)but-2-enoic acid methyl ester as a light orange oil which was a mixture of geometric isomers.

To a chilled (0°C) suspension of 4.3 g (22.58 mmol) of copper (I) iodide (purified by Soxhlet extraction with THF) in 100 mL of diethyl ether was added 26 mL (41.60 mmol) of a 1.6 M solution of methyl lithium in ether over a 15 minute period. After the addition, the mixture stirred for 10 min and was then cooled to -25°C and a solution of 4.0 g (15.19 mmol) of 2-

cyano-3-(4-fluoro-2-methoxyphenyl)but-2-enoic acid methyl ester in 50 mL of diethyl ether was added over a 20 minute period. The mixture stirred at -25°C for 30 minutes and was then allowed to warm to room temperature. The reaction was monitored by proton NMR. After 1.5 hours, an aliquot partitioned between EtOAc and 1 N aqueous HCl indicated starting material was gone and desired product was present. The reaction was cautiously poured into brine and then saturated aqueous ammonium chloride was added followed by 1 N aqueous HCl and EtOAc. The mixture was filtered through diatomaceous earth and the aqueous layer was separated and extracted with three 50 mL portions of EtOAc. The combined organic layers were washed with 30 mL of 1 N aqueous HCl, 30 mL of brine, and three 25 mL portions of saturated aqueous sodium bicarbonate, dried over magnesium sulfate, filtered, and concentrated to afford 4.2 g (99%) of 2-cyano-3-(4-fluoro-2-methoxyphenyl)-3-methylbutyric acid methyl ester.

A mixture of 4.2 g (15.03 mmol) of 2-cyano-3-(4-fluoro-2-methoxyphenyl)-3-methylbutyric acid methyl ester and 2.5 g (42.77 mmol) of sodium chloride in 40 mL of DMSO with 2 mL of water was warmed to reflux. Gas evolution was clearly evident early in the reaction. After 4 hours, the reaction was cooled and diluted with 100 mL of brine and extracted with four 75 mL portions of EtOAc. The combined organic layers were washed with six 50 mL portions of brine, dried over magnesium sulfate, filtered, and concentrated to afford an oil which solidified under vacuum. The tan solid was triturated with hexanes and collected by filtration to afford 2.52 g (81%) of 3-(4-fluoro-2-methoxyphenyl)-3-methylbutyronitrile, m.p. 80°C-83°C.

To a chilled (-40°C) solution of 2 g (9.65 mmol) of 3-(4-fluoro-2-methoxyphenyl)-3-methylbutyronitrile in 20 mL of dichloromethane was added 20 mL (20 mmol) of a 1 M solution of diisobutylaluminum hydride in dichloromethane over a 10 minute period. The mixture was then allowed to warm to room temperature. After 4 hours, the mixture was cautiously added to 1 N aqueous HCl and concentrated *in vacuo* to remove the dichloromethane. The residue was extracted with three 40 mL portions of EtOAc. The combined organic layers were washed with 30 mL of 1 N aqueous HCl, two 30 mL portions of brine, 30 mL of saturated aqueous sodium bicarbonate, dried over magnesium sulfate, filtered, and concentrated to afford 1.89 g (93%) of 3-(4-fluoro-2-methoxyphenyl)-3-methylbutyraldehyde as an oil which was used without further purification.

To 1.89 g (8.99 mmol) of 3-(4-fluoro-2-methoxyphenyl)-3-methylbutyraldehyde was added 25 mL (12.5 mmol) of a 0.5 M solution of trimethyl(trifluoromethyl)silane in tetrahydrofuran and 2 mL (2 mmol) of a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran was added over a 2 minute period. The mixture stirred for 30 minutes and then an additional 8 mL (8 mmol) of a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran was added. The mixture was then diluted with water and extracted with three 25 mL portions of EtOAc. The combined organic layers were washed with three 20 mL portions of 1 N aqueous HCl, three 20 mL portions of brine, and three 20 mL portions of saturated aqueous sodium bicarbonate, dried over magnesium sulfate, filtered, and concentrated to afford 2.78 g of 1,1,1-trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol as an oil. The oil was dried under high vacuum to a constant weight of 2.36 g (93%) and was used without further purification.

To a solution of 2.3 g (8.42 mmol) of 1,1,1-trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol in 40 mL of dichloromethane was added the 4.96 (11.70 mmol) of Dess-Martin periodinane. After 1 hour, the mixture was concentrated and diluted with ether-hexanes (1:9) and filtered through a pad of silica gel, washing with 1:1 ether-hexanes. Use of a second pad of silica gel washing with EtOAc-hexanes (1:9) afforded the title compound as an oil. The product was dried under vacuum to a constant weight of 2 g (85%).

The following trifluoromethyl ketones were also prepared by the method of Example 26:

4-(3,5-Dimethoxyphenyl)-1,1,1-trifluoro-4-methylpentan-2-one;

1,1,1-Trifluoro-4-(1-methoxynaphthalen-2-yl)-4-methylpentan-2-one;

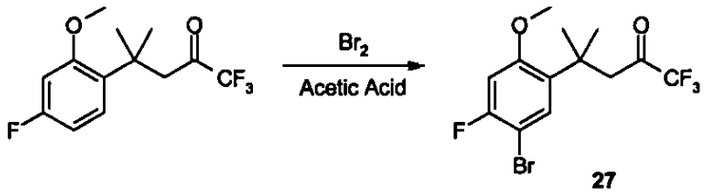
1,1,1-Trifluoro-4-methyl-4-naphthalen-2-ylpentan-2-one;

1,1,1-Trifluoro-4-(3-methoxyphenyl)-4-methylpentan-2-one; and

1,1,1-Trifluoro-4-methyl-4-(3-trifluoromethylphenyl)pentan-2-one.

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Example 27: Synthesis of 4-(5-bromo-4-fluoro-2-methoxyphenyl)-1,1,1-trifluoro-4-methylpentan-2-one



27

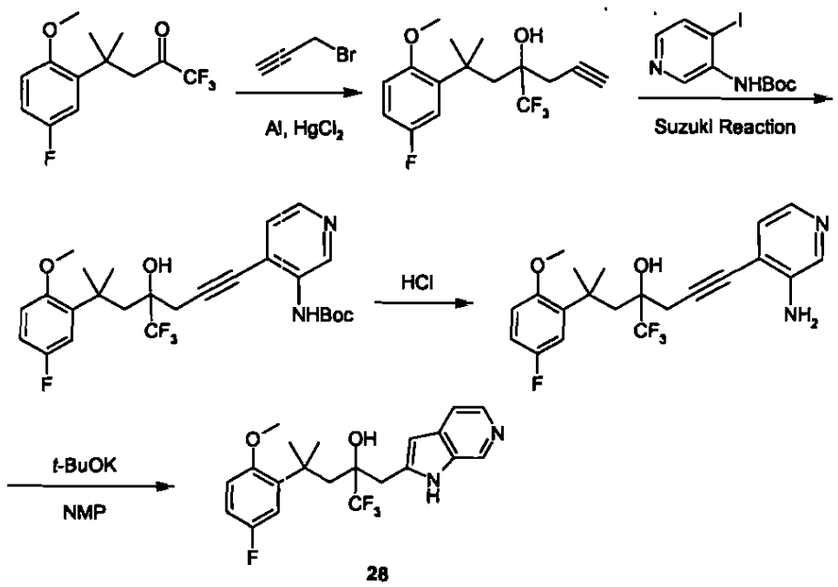
To a solution of 300 mg (1.078 mmol) of 1,1,1-trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methylpentan-2-one (Example 26) in 0.5 mL of acetic acid was added 70 μL (1.35 mmol) of bromine. The reaction was monitored by TLC (EtOAc-hexanes (1:9)) by partitioning an aliquot between saturated aqueous sodium bicarbonate and EtOAc. A new slightly more polar product was observed. The reaction was made basic with saturated aqueous sodium bicarbonate and extracted with three 15 mL portion of EtOAc. The combined organic layers were washed with two 10 mL portions of saturated aqueous sodium bicarbonate and 10 mL of brine, dried over magnesium sulfate, filtered, and concentrated. The residue was dissolved in hexanes and passed through a pad of silica gel, eluting with EtOAc-hexanes (0.5:99.5) to afford 375 mg (97%) of the title compound.

The following compounds were prepared by the method of Example 27:

4-(5-Bromo-2,3-dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methylpentan-2-one; and

4-(7-Bromo-2,3-dihydrobenzofuran-5-yl)-1,1,1-trifluoro-4-methylpentan-2-one.

Example 28: Synthesis of 1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol



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Aluminum amalgam was prepared from aluminum foil (1.16g, 14.4 mmol) and mercuric chloride (12 mg, catalytic amount) in dry THF (20 mL) by vigorously stirring the mixture at room temperature for 1 hour under an argon atmosphere. A solution of propargyl bromide (4.80 mL, 80 wt.% in toluene, 43.1 mmol) in dry THF (25 mL) was slowly added to a stirred suspension maintaining a temperature of 30°C-40°C, and after addition, stirring at 40°C was continued until a dark gray solution was obtained (*ca.* 1 hour). The propargyl aluminum sesquibromide solution was added to a solution of the trifluoromethylketone (4.0 g, 14.4 mmol) in dry ether (150 mL) at -78°C. The reaction mixture was stirred at this temperature for 3 hours, and then was allowed to warm to room temperature, at which time it was stirred for 12 hours. The reaction mixture was then poured into 20 mL of ice water and extracted with four 30 mL portions of ether. The combined extracts were washed with 20 mL of brine, dried over magnesium sulfate, and concentrated. The residual oil was subjected to column chromatography over silica gel to afford pure propargylated compound as an oil.

A mixture of the above acetylene intermediate (656 mg, 2.06 mmol), (4-iodopyridin-3-yl)-carbamic acid *tert*-butyl ester (600 mg, 1.87 mmol) (see T.A. Kelly *et al.*, J. Org. Chem., 1995, 60, 1877), bis(triphenylphosphine)palladium(II) chloride catalyst (72 mg, 0.1 mmol) and copper (I) iodide (39 mg, 0.2 mmol) in anhydrous triethylamine (6 mL) and dry DMF (1 mL) was stirred at room temperature for 20 hours. The reaction mixture was then diluted with 50

mL of ether and washed with 20 mL of aqueous saturated ammonium chloride solution and 20 mL of brine. The organic layer was dried over magnesium sulfate and concentrated *in vacuo*. Column chromatography over silica gel with hexanes-EtOAc (5:1 to 1:1) provided {4-[6-(5-fluoro-2-methoxyphenyl)-4-hydroxy-6-methyl-4-trifluoromethylhept-1-ynyl]pyridin-3-yl}carbamic acid *tert*-butyl ester as a foam.

The above *tert*-butyl ester (480 mg, 0.94 mmol) was treated with a hydrogen chloride solution (2M in ether, 15 mL) and stirred at room temperature for 6 hours. Then the solution was concentrated *in vacuo* to yield the crude amine as oil, which was crashed out with hexanes to give the amine a yellow solid.

To the above crude amine product (742 mg, 1.81 mmol) in anhydrous 1-methyl-2-pyrrolidinone (NMP) (7 mL) was added *t*-BuOK (449 mg, 112 mmol) and the reaction mixture was stirred under an argon atmosphere at room temperature for 24 hours. The mixture was diluted with 30 mL of ether and washed with four 10 mL portions of water, and the combined aqueous layers were re-extracted with 20 mL of ether, while the combined organic layers were washed with 10 mL of brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residual oil was subjected to column chromatography over silica gel (methylene chloride-1% to 10% MeOH) to afford 1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol as yellowish crystals.

Resolution to the (+)- and (-)-enantiomers was accomplished by chiral HPLC on a CHIRALCEL™ OD column, eluting with 15% to 25% isopropanol-hexanes.

Assessment of Biological Properties

Compounds of the invention were evaluated for binding to the steroid receptor by a fluorescence polarization competitive binding assay. Detailed descriptions for preparation of recombinant glucocorticoid receptor (GR) complex used in the assay is described in U.S. provisional application No. 60/291,877, filed May 18, 2001, and incorporated herein by reference in its entirety. Preparation of the tetramethyl rhodamine (TAMRA)-labeled dexamethasone probe was accomplished using a standard literature procedure (M. Pons *et al.*, J. Steroid Biochem., 1985, 22, pp. 267-273).

A. Glucocorticoid Receptor Competitive Binding Assay

Step 1. Characterization of the Fluorescent Probe

The wavelengths for maximum excitation and emission of the fluorescent probe should first be measured. An example of such a probe is rhodamine (TAMRA)-labeled dexamethasone.

The affinity of the probe for the steroid receptor was then determined in a titration experiment. The fluorescence polarization value of the probe in assay buffer was measured on an SLM-8100 fluorometer using the excitation and emission maximum values described above. Aliquots of expression vector lysate were added and fluorescence polarization was measured after each addition until no further change in polarization value was observed. Non-linear least squares regression analysis was used to calculate the dissociation constant of the probe from the polarization values obtained for lysate binding to the probe.

Step 2. Screening for Inhibitors of Probe Binding

This assay uses fluorescence polarization (FP) to quantitate the ability of test compounds to compete with tetramethyl rhodamine (TAMRA)-labeled dexamethasone for binding to a human glucocorticoid receptor (GR) complex prepared from an insect expression system. The assay buffer was: 10 mM TES, 50 mM KCl, 20 mM $Na_2MoO_4 \cdot 2H_2O$, 1.5 mM EDTA, 0.04% w/v CHAPS, 10% v/v glycerol, 1 mM dithiothreitol, pH 7.4. Test compounds were dissolved to 1 mM in neat DMSO and then further diluted to 10x assay concentration in assay buffer supplemented with 10% v/v DMSO. Test compounds were serially diluted at 10x assay concentrations in 10% DMSO-containing buffer in 96-well polypropylene plates. Binding reaction mixtures were prepared in 96-well black Dynex microtiter plates by sequential addition of the following assay components to each well: 15 µL of 10x test compound solution, 85 µL of GR-containing baculovirus lysate diluted 1:170 in assay buffer, and 50 µL of 15 nM TAMRA-labeled dexamethasone. Positive controls were reaction mixtures containing no test compound; negative controls (blanks) were reaction mixtures containing 0.7 µM to 2 µM dexamethasone. The binding reactions were incubated for 1 hour at room temperature and then read for fluorescence polarization in the LJL Analyst set to 550 nm excitation and 580 nm emission, with the Rhodamine 561 dichroic mirror installed. IC_{50} values were determined by iterative non-linear curve fitting of the FP signal data to a 4-parameter logistic equation.

Compounds found to bind to the glucocorticoid receptor may be evaluated for binding to the progesterone receptor (PR), estrogen receptor (ER), and mineralocorticoid receptors (MR) to evaluate the compound's selectivity for GR. The protocols for PR and MR are identical to the above GR method, with the following exceptions: PR insect cell lysate is diluted 1:7.1 and MR lysate diluted 1:9.4. PR probe is TAMRA-labeled mifepristone, used at a final concentration of 5 nM in the assay, and the negative controls (blanks) were reactions containing mifepristone at 0.7 μM to 2 μM.

The ER protocol is similar to the above protocols, but uses PanVera kit receptor, fluorescein-labeled probe. The assay components are made in the same volumes as above, to produce final assay concentrations for ER of 15 nM and ES2 probe of 1 nM. In addition, the component order of addition is modified from the above assays: probe is added to the plate first, followed by receptor and test compound. The plates are read in the LJL Analyst set to 485 nm excitation and 530 nm emission, with the Flucrescein 505 dichroic mirror installed.

Compounds found to bind to the glucocorticoid receptor may be evaluated for dissociation of transactivation and transrepression by assays cited in the Background of the Invention (C.M. Bamberger and H.M. Schulte, Eur. J. Clin. Invest., 2000, 30 (suppl. 3) 6-9) or by the assays described below.

B. Glucocorticoid Receptor Cell Assays

1. Induction of Aromatase in Fibroblasts (Cell Assay for Transactivation)

Dexamethasone, a synthetic ligand to the glucocorticoid receptor (GR), induces expression of aromatase in human foreskin fibroblast cells. The activity of aromatase is measured by the conversion of testosterone to estradiol in culture media. Compounds that exhibit binding to GR are evaluated for their ability to induce aromatase activity in human foreskin fibroblasts.

Human foreskin fibroblast cells (ATCC Cat. No. CRL-2429, designation CCD112SK) are plated on 96 well plates at 50,000 cells per well 5 days before use, in Iscove's Modified Dulbecco's Media (GibcoBRL Life Technologies Cat No. 12440-053) supplemented with 10% charcoal filtered FBS (Clonetech Cat No. SH30068) and Gentamycin (GibcoBRL Life

Technologies Cat. No. 15710-064). On the day of the experiment, the media in the wells is replaced with fresh media. Cells are treated with test compounds to final concentrations of 10^{-5} M to 10^{-8} M, and testosterone to a final concentration of 300 ng/mL. Each well has a total volume of 100 µL. Samples are made in duplicates. Control wells include: (a) wells that receive testosterone only, and (b) wells that receive testosterone plus 2 µM of dexamethasone to provide maximum induction of aromatase. Plates are incubated at 37°C overnight (15 to 18 hours), and supernatants are harvested at the end of incubation. Estradiol in the supernatant is measured using ELISA kits for estradiol (made by ALPCO, obtained from American Laboratory Products Cat. No. 020-DR-2693) according to the manufacture's instruction. The amount of estradiol is inversely proportional to the ELISA signals in each well. The extent of aromatase induction by test compounds is expressed as a relative percentage to dexamethasone. EC_{50} values of test compounds are derived by non-linear curve fitting.

2. Inhibition of IL-6 Production in Fibroblasts (Cell Assay for Transrepression)

Human foreskin fibroblast cells produce IL-6 in response to stimulation by pro-inflammatory cytokine IL-1. This inflammatory response, as measured by the production of IL-6, can be effectively inhibited by dexamethasone, a synthetic ligand to the glucocorticoid receptor (GR). Compounds that exhibit binding to GR are evaluated for their ability to inhibit IL-6 production in human foreskin fibroblasts.

Human foreskin fibroblast cells (ATCC Cat. No. CRL-2429) are plated on 96 well plates at 5,000 cells per well the day before use, in Iscove's Modified Dulbecco's Media (GibcoBRL Life Technologies Cat. No. 12440-053) supplemented with 10% charcoal filtered FBS (Clonetech Cat. No. SH30068) and Gentamycin (GibcoBRL Life Technologies Cat. No. 15710-064). On the next day, media in the wells is replaced with fresh media. Cells are treated with IL-1 (rhIL-1α, R&D Systems Cat. No. 200-LA) to a final concentration of 1 ng/mL, and with test compounds to final concentrations of 10^{-5} M to 10^{-8} M, in a total volume of 200 µL per well. Samples are done in duplicates. Background control wells do not receive test compounds or IL-1. Positive control wells receive IL-1 only and represent maximum (or 100%) amount of IL-6 production. Plates are incubated at 37°C overnight (15 to 18 hours), and supernatants are harvested at the end of incubation. IL-6 levels in the supernatants are determined by the ELISA kits for IL-6 (MedSystems Diagnostics GmbH, Vienna, Austria, Cat. No. BMS213TEN)

according to manufacture's instructions. The extent of inhibition of IL-6 by test compounds is expressed in percentage relative to positive controls. IC_{50} values of test compounds are derived by non-linear curve fitting.

Evaluation of agonist or antagonist activity of compounds binding to the glucocorticoid receptor may be determined by any of the assays.

3. Modulation of Tyrosine Aminotransferase (TAT) Induction in Rat Hepatoma Cells

Testing of compounds for agonist or antagonist activity in induction of tyrosine aminotransferase (TAT) in rat hepatoma cells.

H4-II-E-C3 cells were incubated overnight in 96 well plates (20,000 cells/100 µL/well) in MEM medium containing 10% heat inactivated FBS and 1% nonessential amino acids. On the next day, cells were stimulated with the indicated concentrations of dexamethasone or test compound (dissolved in DMSO, final DMSO concentration 0.2%) for 18 hours. Control cells were treated with 0.2% DMSO. After 18 hours, the cells were lysed in a buffer containing 0.1% Triton X-100 and the TAT activity was measured in a photometric assay using tyrosine and alpha-ketoglutarate as substrates.

For measuring antagonist activity, the hepatoma cells were pre-stimulated by addition of dexamethasone (concentration ranges from 3×10^{-9} M to 3×10^{-8} M) shortly before the test compound was applied to the cells. The steroidal non-selective GR/PR antagonist mifepristone was used as control.

4. Modulation of MMTV-Luc Induction in HeLa Cells

Testing of compounds for agonist or antagonist activity in stimulation of MMTV-(mouse mammary tumor virus) promoter in HeLa cells.

HeLa cells were stably co-transfected with the pHHLuc-plasmid containing a fragment of the MMTV-LTR (-200 to +100 relative to the transcription start site) cloned in front of the luciferase gene (Norden, 1988) and the pcDNA3.1 plasmid (Invitrogen) constitutively

expressing the resistance for the selective antibiotic GENETICIN®. Clones with best induction of the MMTV-promoter were selected and used for further experiments.

Cells were cultured overnight in DMEM medium without phenol red, supplemented with 3% CCS (charcoal treated calf serum) and then transferred to 96 well plates (15,000 cells/100 µL/well). On the next day, activation of the MMTV-promoter was stimulated by addition of test compound or dexamethasone dissolved in DMSO (final concentration 0.2%). Control cells were treated with DMSO only. After 18 hours, the cells were lysed with cell lysis reagent (Promega, Cat. No. E1531), luciferase assay reagent (Promega, Cat. No. E1501) was added and the glow luminescence was measured using a luminometer (BMG, Offenburg).

For measuring antagonist activity, the MMTV-promoter was pre-stimulated by adding dexamethasone (3 x 10^{-9} M to 3 x 10^{-8} M) shortly before the test compound was applied to the cells. The steroidal non-selective GR/PR antagonist mifepristone was used as control.

5. Modulation of IL-8 Production in U937 Cells

Testing of compounds for agonist or antagonist activity in GR-mediated inhibition of LPS-induced IL-8 secretion in U-937 cells.

U-937 cells were incubated for 2 to 4 days in RPMI1640 medium containing 10% CCS (charcoal treated calf serum). The cells were transferred to 96 well plates (40,000 cells/100 µL/well) and stimulated with 1 µg/mL LPS (dissolved in PBS) in the presence or absence of dexamethasone or test compound (dissolved in DMSO, final concentration 0.2%). Control cells were treated with 0.2% DMSO. After 18 hours, the IL-8 concentration in the cell supernatant was measured by ELISA, using the "OptEIA human IL-8 set" (Pharmingen, Cat. No. 2654KI).

For measuring antagonist activity, the LPS-induced IL-8 secretion was inhibited by adding dexamethasone (3 x 10^{-9} M to 3 x 10^{-8} M) shortly before the test compound was applied to the cells. The steroidal non-selective GR/PR antagonist mifepristone was used as control.

6. Modulation of ICAM-Luc Expression in HeLa Cells

Testing of compounds for agonist or antagonist activity in inhibition of TNF-alpha-induced activation of the ICAM-promoter in HeLa cells.

HeLa cells were stably co-transfected with a plasmid containing a 1.3 kb fragment of the human ICAM-promoter (-1353 to -9 relative to the transcription start site, Ledebur and Parks, 1995) cloned in front of the luciferase gene and the pcDNA3.1 plasmid (Invitrogen) which constitutively expresses the resistance for the antibiotic GENETICIN®. Clones with best induction of the ICAM-promoter were selected and used for further experiments. Cells were transferred to 96 well plates (15,000 cells/100 µL/well) in DMEM medium supplemented with 3% CCS. On the following day the activation of the ICAM-promoter was induced by addition of 10 ng/mL recombinant TNF-alpha (R&D System, Cat. No. 210-TA). Simultaneously the cells were treated with the test compound or dexamethasone (dissolved in DMSO, final concentration 0.2%). Control cells were treated with DMSO only. After 18 hours, the cells were lysed with cell lysis reagent (Promega, Cat. No. E1531), luciferase assay reagent (Promega, Cat. No. E1501) was added and glow luminescence was measured using a luminometer (BMG, Offenburg).

For measuring antagonist activity, the TNF-alpha-induced activation of the ICAM-promoter was inhibited by adding dexamethasone (3×10^{-9} M to 3×10^{-8} M) shortly before the test compound was applied to the cells. The steroidal non-selective GR/PR antagonist mifepristone was used as control.

In general, the preferred potency range in the above assays is between 0.1 nM and 10 µM, the more preferred potency range is 0.1 nM to 1 µM, and the most preferred potency range is 0.1 nM to 100 nM.

Representative compounds of the invention have been tested and have shown activity as modulators of the glucocorticoid receptor function in one or more of the above assays. For example, the following compounds of the invention of Formula (IA) have demonstrated potent activity in the GR binding assay:

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-(2,6-Dichloropyridin-4-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-[3-(2,6-Dichloropyridin-4-ylmethyl)-4,4,4-trifluoro-3-hydroxy-1,1-dimethylbutyl]-4-fluorophenol;

4-(5-Bromo-2,3-dihydrobenzofuran-7-yl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-(1*H*-Benzimidazol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorophenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(quinolin-4-ylmethyl)pentan-2-ol;

4-(2,3-dihydro-5-cyanobenzofuran-7-yl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(2-chloropyridin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-hydroxyphenyl)-4-methyl-2-(2-chloropyridin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(2-chloroquinolin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-hydroxyphenyl)-4-methyl-2-(2-chloroquinolin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-(4-methoxyphenyl)-4-methylpentan-2-ol;

4-[4,4,4-Trifluoro-3-hydroxy-3-(1*H*-indol-2-ylmethyl)-1,1-dimethylbutyl]phenol;

1,1,1-Trifluoro-2-(5-fluoro-1*H*-indol-2-ylmethyl)-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

4-(2,3-dihydrobenzofuran-7-yl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(2-bromopyridin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(7-methyl-1*H*-benzoimidazol-2-ylmethyl)pentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(4-methyl-1*H*-indol-2-ylmethyl)butyl]phenol;

4-Fluoro-2-[4,4,4-trifluoro-3-(7-fluoro-1*H*-indol-2-ylmethyl)-3-hydroxy-1,1-dimethylbutyl]phenol;

1,1,1-Trifluoro-2-(6-fluoro-1*H*-benzoimidazol-2-ylmethyl)-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

2-(6,7-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

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4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(5-Bromo-2,3-dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(3-Ethyl-2-methoxyphenyl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

2-Ethyl-6-(4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

2-Ethyl-6-[4,4,4-trifluoro-3-hydroxy-3-(1*H*-indol-2-ylmethyl)-1,1-dimethylbutyl]phenol;

2-(5,7-Dimethyl-1*H*-benzoimidazol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

2-[3-(5,7-Dimethyl-1*H*-benzoimidazol-2-ylmethyl)-4,4,4-trifluoro-3-hydroxy-1,1-dimethylbutyl]-4-fluorophenol;

1,1,1-Trifluoro-4-(3-methoxyphenyl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-(3-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-4-methyl-2-(4-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-4-methyl-2-(4-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorophenyl)-4-methyl-2-(4-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-methyl-2-quinolin-4-ylmethyl-4-(3-trifluoromethylphenyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-4-methyl-2-(7-methyl-1*H*-benzoimidazol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-(3-trifluoromethylphenyl)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

5-Fluoro-2-(4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

4-(5-Bromo-4-fluoro-2-methoxyphenyl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

2-(2-Phenyl-4-methylimidazol-1-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihydrobenzofuran-7-yl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

2-(2-Phenylimidazol-1-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihydrobenzofuran-7-yl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

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1,1,1-Trifluoro-4-methyl-4-(5-methyl-2,3-dihydrobenzofuran-7-yl)-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-phenylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-(5-methyl-2,3-dihydrobenzofuran-7-yl)pentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-*m*-tolylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-naphthalen-2-ylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-*o*-tolylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-*p*-tolylpentan-2-ol;

4-(2,3-Dihydrobenzofuran-5-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(7-Bromo-2,3-dihydrobenzofuran-5-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(2,3-Dihydrobenzofuran-5-yl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(1-methoxynaphthalen-2-yl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

2-(4,4,4-Trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)naphthalen-1-ol;

1,1,1-Trifluoro-4-methyl-4-naphthalen-2-yl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-(1-methoxynaphthalen-2-yl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-methyl-2-quinolin-4-ylmethyl-4-*p*-tolylpentan-2-ol;

4-Chroman-8-yl-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-4-methyl-4-phenyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(6-Bromochroman-8-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*b*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*b*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorophenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-methyl-4-phenyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(7-fluoroquinolin-4-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-2-(7-fluoroquinolin-4-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-2-(5-fluoroquinolin-4-ylmethyl)-4-methylpentan-2-ol;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

2-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

2-[4-(5-Fluoro-2-methylphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

1,1,1-Trifluoro-4-(2-methoxyphenyl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-(2-methoxyphenyl)-4-methylpentan-2-ol;

2-[4-(5-Fluoro-2,3-dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

4-(5-Bromo-2-methoxyphenyl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(5-Bromo-2-methoxyphenyl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-(4,4,4-Trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

1,1,1-Trifluoro-4-methyl-4-phenyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-[4-(5-Bromo-2,3-dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

4-Bromo-2-(4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-[4-(4-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethyl-pentyl]-1*H*-indole-3-carbonitrile;

2-(2-Hydroxy-4-methyl-4-phenyl-2-trifluoromethylpentyl)-4-methyl-1*H*-indole-6-carbonitrile;

2-[4-(3-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

2-[4-(4-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

2-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-methyl-4-phenyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-(2-Hydroxy-4-methyl-4-phenyl-2-trifluoromethylpentyl)-1*H*-indole-5-carbonitrile;

2-[4-(3-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

2-[4-(4-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-(5,6,7,8-tetrahydroquinolin-4-ylmethyl)pentan-2-ol;

1-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-(2-Hydroxy-4-methyl-4-phenyl-2-trifluoromethylpentyl)-1*H*-indole-3-carbonitrile;

5-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)butyl]phenol;

2-[4-(4-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(3-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(4-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(5-Fluoro-2-methylphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)butyl]phenol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-methyl-4-phenylpentan-2-ol;

2-[4-(4-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carboxylic acid methyl ester;

1-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(3-methyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(3-methoxyphenyl)-4-methyl-2-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

2-[2-Hydroxy-4-(3-methoxyphenyl)-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)butyl]phenol;

5-Fluoro-2-[4,4,4-trifluoro-3-(7-fluoro-1*H*-indol-2-ylmethyl)-3-hydroxy-1,1-dimethylbutyl]phenol;

2-[4-(5-Fluoro-2-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(3-methyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)butyl]phenol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-thiophen-3-ylpentan-2-ol;

1,1,1-Trifluoro-4-methyl-2-quinolin-4-ylmethyl-4-thiophen-3-ylpentan-2-ol;

5-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)butyl]phenol;

1,1,1-Trifluoro-4-(3-fluorophenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

3-(4,4,4-Trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

2-[4-(5-Bromo-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carboxylic acid methyl ester;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carboxylic acid methyl ester;

4-(2,6-Dimethylphenyl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

3-[4,4,4-Trifluoro-3-hydroxy-3-(1*H*-indol-2-ylmethyl)-1,1-dimethylbutyl]phenol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihydrobenzofuran-7-yl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-[2-Hydroxy-4-(3-methoxyphenyl)-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile; and

2-[4-(5-Bromo-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile.

The following compounds of the invention of Formula (IB) have demonstrated potent activity in the GR binding assay:

5-(5-Fluoro-2-methoxyphenyl)-3-(benzimidazol-2-ylmethyl)-2,2,5-trimethylhexan-3-ol;

4-(5-Fluoro-2-methoxyphenyl)-1-fluoro-2-(indol-2-ylmethyl)-4-methylpentan-3-ol;

1-Cyclopropyl-4-(5-fluoro-2-methoxyphenyl)-2-(indol-2-ylmethyl)-4-methylpentan-2-ol;

5-(5-Fluoro-2-methoxyphenyl)-3-(indol-2-ylmethyl)-2,5-dimethylhexan-3-ol;

5-(5-Fluoro-2-methoxyphenyl)-3-(indol-2-ylmethyl)-5-methylhexan-3-ol; and

2-Cyclopropyl-4-(5-fluoro-2-methoxyphenyl)-4-methyl-1-(1*H*-pyrrolo[2,3-c]pyridin-2-yl)pentan-2-ol.

In addition, the following compounds of the invention of Formula (IA) have been tested and have shown activity as potent agonists of the glucocorticoid receptor function in one or more of the above assays:

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-(2,6-Dichloropyridin-4-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

4-(5-Bromo-2,3-dihydrobenzofuran-7-yl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(quinolin-4-ylmethyl)pentan-2-ol;

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1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

4-(2,3-dihydrobenzofuran-7-yl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(4-methyl-1*H*-indol-2-ylmethyl)butyl]phenol;

4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(5-Bromo-2,3-dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

2-[3-(5,7-Dimethyl-1*H*-benzoimidazol-2-ylmethyl)-4,4,4-trifluoro-3-hydroxy-1,1-dimethylbutyl]-4-fluorophenol;

1,1,1-Trifluoro-4-(3-methoxyphenyl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-(3-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-4-methyl-2-(4-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-4-methyl-2-(4-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorophenyl)-4-methyl-2-(4-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-methyl-2-quinolin-4-ylmethyl-4-(3-trifluoromethylphenyl)pentan-2-ol;

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1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-(3-trifluoromethylphenyl)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

5-Fluoro-2-(4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

4-(5-Bromo-4-fluoro-2-methoxyphenyl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihydrobenzofuran-7-yl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihydrobenzofuran-7-yl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-methyl-4-(5-methyl-2,3-dihydrobenzofuran-7-yl)-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-(5-methyl-2,3-dihydrobenzofuran-7-yl)pentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-*m*-tolylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-*o*-tolylpentan-2-ol;

4-(7-Bromo-2,3-dihydrobenzofuran-5-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-c]pyridin-2-ylmethyl)pentan-2-ol;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

1,1,1-Trifluoro-4-methyl-4-phenyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(7-fluoroquinolin-4-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-2-(5-fluoroquinolin-4-ylmethyl)-4-methylpentan-2-ol;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

2-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

2-[4-(5-Fluoro-2-methylphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

1,1,1-Trifluoro-4-(2-methoxyphenyl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-(2-methoxyphenyl)-4-methylpentan-2-ol;

2-[4-(5-Fluoro-2,3-dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

4-(5-Bromo-2-methoxyphenyl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(5-Bromo-2-methoxyphenyl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-(4,4,4-Trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

1,1,1-Trifluoro-4-methyl-4-phenyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-[4-(5-Bromo-2,3-dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

4-Bromo-2-(4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-[4-(4-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethyl-pentyl]-1*H*-indole-3-carbonitrile;

2-(2-Hydroxy-4-methyl-4-phenyl-2-trifluoromethylpentyl)-4-methyl-1*H*-indole-6-carbonitrile;

2-[4-(3-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

2-[4-(4-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

2-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-methyl-4-phenyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-(2-Hydroxy-4-methyl-4-phenyl-2-trifluoromethylpentyl)-1*H*-indole-5-carbonitrile;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-(5,6,7,8-tetrahydroquinolin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

5-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)butyl]phenol;

2-[4-(4-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(4-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(5-Fluoro-2-methylphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)butyl]phenol;

1-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)butyl]phenol;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(3-methyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-[4-(5-Fluoro-2-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;
2-[2-Hydroxy-4-(3-methoxyphenyl)-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile; and

2-[4-(5-Bromo-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile.

The following compounds of the invention of Formula (IB) have been tested and have shown activity as agonists of the glucocorticoid receptor function in one or more of the above assays:

2-Cyclopropyl-4-(5-fluoro-2-methoxyphenyl)-1-(1*H*-indol-2-yl)-4-methylpentan-2-ol; and

2-Cyclopropyl-4-(5-fluoro-2-methoxyphenyl)-4-methyl-1-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)pentan-2-ol.

The invention also provides methods of modulating the glucocorticoid receptor function in a patient comprising administering to the patient a compound according to the invention. If the purpose of modulating the glucocorticoid receptor function in a patient is to treat a disease-state or condition, the administration preferably comprises a therapeutically or pharmaceutically effective amount of a pharmaceutically acceptable compound according to the invention. If the purpose of modulating the glucocorticoid receptor function in a patient is for a diagnostic or other purpose (e.g., to determine the patient's suitability for therapy or sensitivity to various

sub-therapeutic doses of the compounds according to the invention), the administration preferably comprises an effective amount of a compound according to the invention, that is, the amount necessary to obtain the desired effect or degree of modulation.

Methods of Therapeutic Use

As pointed out above, the compounds of the invention are useful in modulating the glucocorticoid receptor function. In doing so, these compounds have therapeutic use in treating disease-states and conditions mediated by the glucocorticoid receptor function or that would benefit from modulation of the glucocorticoid receptor function.

As the compounds of the invention modulate the glucocorticoid receptor function, they have very useful anti-inflammatory and antiallergic, immune-suppressive, and anti-proliferative activity and they can be used in patients as drugs, particularly in the form of pharmaceutical compositions as set forth below, for the treatment of disease-states and conditions.

The agonist compounds according to the invention can be used in patients as drugs for the treatment of the following disease-states or indications that are accompanied by inflammatory, allergic, and/or proliferative processes:

(i) Lung diseases: chronic, obstructive lung diseases of any genesis, particularly bronchial asthma and chronic obstructive pulmonary disease (COPD); adult respiratory distress syndrome (ARDS); bronchiectasis; bronchitis of various genesis; all forms of restrictive lung diseases, particularly allergic alveolitis; all forms of lung edema, particularly toxic lung edema; all forms of interstitial lung diseases of any genesis, e.g., radiation pneumonitis; and sarcoidosis and granulomatoses, particularly Boeck disease.

(ii) Rheumatic diseases or autoimmune diseases or joint diseases: all forms of rheumatic diseases, especially rheumatoid arthritis, acute rheumatic fever, and polymyalgia rheumatica; reactive arthritis; rheumatic soft tissue diseases; inflammatory soft tissue diseases of other genesis; arthritic symptoms in degenerative joint diseases (arthroses); traumatic arthritis; collagenoses of any genesis, e.g., systemic lupus erythematosus, scleroderma, polymyositis, dermatomyositis, Sjögren syndrome, Still disease, and Felty syndrome;

(iii) Allergic diseases: all forms of allergic reactions, e.g., angioneurotic edema, hay fever, insect bites, allergic reactions to drugs, blood derivatives, contrast agents, etc., anaphylactic shock (anaphylaxis), urticaria, angioneurotic edema, and contact dermatitis;

(iv) Vasculitis diseases: panarteritis nodosa, polyarteritis nodosa, arteritis temporalis, Wegner granulomatosis, giant cell arthritis, and erythema nodosum;

(v) Dermatological diseases: atopic dermatitis, particularly in children; psoriasis; pityriasis rubra pilaris; erythematous diseases triggered by various noxa, e.g., rays, chemicals, burns, etc.; bullous dermatoses; diseases of the lichenoid complex; pruritus (e.g., of allergic genesis); seborrheic dermatitis; rosacea; pemphigus vulgaris; erythema multiforme exudativum; balanitis; vulvitis; hair loss, such as occurs in alopecia areata; and cutaneous T cell lymphomas;

(vi) Renal diseases: nephrotic syndrome; and all types of nephritis, e.g., glomerulonephritis;

(vii) Hepatic diseases: acute liver cell disintegration; acute hepatitis of various genesis, e.g., viral, toxic, drug-induced; and chronically aggressive and/or chronically intermittent hepatitis;

(viii) Gastrointestinal diseases: inflammatory bowel diseases, e.g., regional enteritis (Crohn disease), colitis ulcerosa; gastritis; peptic esophagitis (refluxoesophagitis); and gastroenteritis of other genesis, e.g., nontropical sprue;

(ix) Proctological diseases: anal eczema; fissures; hemorrhoids; and idiopathic proctitis;

(x) Eye diseases: allergic keratitis, uveitis, or iritis; conjunctivitis; blepharitis; neuritis nervi optici; choroiditis; and sympathetic ophthalmia;

(xi) Diseases of the ear, nose, and throat (ENT) area: allergic rhinitis or hay fever; otitis externa, e.g., caused by contact eczema, infection, etc.; and otitis media;

(xii) Neurological diseases: brain edema, particularly tumor-related brain edema; multiple sclerosis; acute encephalomyelitis; meningitis; acute spinal cord injury; stroke; and various forms of seizures, e.g., nodding spasms;

(xiii) Blood diseases: acquired hemolytic anemia; and idiopathic thrombocytopenia;

(xiv) Tumor diseases: acute lymphatic leukemia; malignant lymphoma; lymphogranulomatoses; lymphosarcoma; extensive metastases, particularly in mammary, bronchial, and prostatic carcinoma;

(xv) Endocrine diseases: endocrine ophthalmopathy; endocrine orbitopathia; thyrotoxic crisis; Thyroiditis de Quervain; Hashimoto thyroiditis; Morbus Basedow; granulomatous thyroiditis; struma lymphomatosa; and Grave disease;

(xvi) Organ and tissue transplantations and graft-versus-host diseases;

(xvii) Severe states of shock, e.g., septic shock, anaphylactic shock, and systemic inflammatory response syndrome (SIRS);

(xviii) Substitution therapy in: congenital primary adrenal insufficiency, e.g., adrenogenital syndrome; acquired primary adrenal insufficiency, e.g., Addison disease, autoimmune adrenalitis, post-infection, tumors, metastases, etc.; congenital secondary adrenal insufficiency, e.g., congenital hypopituitarism; and acquired secondary adrenal insufficiency, e.g., post-infection, tumors, metastases, etc.;

(xix) Pain of inflammatory genesis, e.g., lumbago; and

(xx) various other disease-states or conditions including type I diabetes (insulin-dependent diabetes), osteoarthritis, Guillain-Barre syndrome, restenosis following percutaneous transluminal coronary angioplasty, Alzheimer disease, acute and chronic pain, atherosclerosis, reperfusion injury, bone resorption diseases, congestive heart failure, myocardial infarction, thermal injury, multiple organ injury secondary to trauma, acute purulent meningitis, necrotizing enterocolitis and syndromes associated with hemodialysis, leukopheresis, and granulocyte transfusion.

In addition, the compounds according to the invention can be used for the treatment of any other disease-states or conditions not mentioned above which have been treated, are treated, or will be treated with synthetic glucocorticoids (see, e.g., H.J. Hatz, Glucocorticoide: Immunologische Grundlagen. Pharmakologie und Therapierichtlinien [Glucocorticoids: Immunological Fundamentals, Pharmacology, and Therapeutic Guidelines], Stuttgart: Verlagsgesellschaft mbH, 1998, which is hereby incorporated by reference in its entirety). Most or all of the indications (i) through (xx) mentioned above are described in detail in H.J. Hatz, Glucocorticoide: Immunologische Grundlagen. Pharmakologie und Therapierichtlinien. Furthermore, the compounds of the invention can also be used to treat disorders other than those listed above or mentioned or discussed herein, including in the Background of the Invention.

The antagonist compounds according to the invention, whether full antagonists or partial antagonists, can be used in patients as drugs for the treatment of the following disease-states or indications, without limitation: type II diabetes (non-insulin-dependent diabetes); obesity; cardiovascular diseases; hypertension; arteriosclerosis; neurological diseases, such as psychosis and depression; adrenal and pituitary tumors; glaucoma; and Cushing syndrome based on an ACTH secreting tumor like pituitary adenoma. In particular, the compounds of the invention are useful for treating obesity and all disease-states and indications related to a deregulated fatty acids metabolism such as hypertension, atherosclerosis, and other cardiovascular diseases. Using the compounds of the invention that are GR antagonists, it should be possible to antagonize both the carbohydrate metabolism and fatty acids metabolism. Thus, the antagonist compounds of the invention are useful in treating all disease-states and conditions that involve increased carbohydrate, protein, and lipid metabolism and would include disease-states and conditions leading to catabolism like muscle frailty (as an example of protein metabolism).

Methods of Diagnostic Use

The compounds of the invention may also be used in diagnostic applications and for commercial and other purposes as standards in competitive binding assays. In such uses, the compounds of the invention may be used in the form of the compounds themselves or they may be modified by attaching a radioisotope, luminescence, fluorescent label or the like in order to obtain a radioisotope, luminescence, or fluorescent probe, as would be known by one of skill in the art and as outlined in Handbook of Fluorescent Probes and Research Chemicals, 6th Edition, R.P. Haugland (ed.), Eugene: Molecular Probes, 1996; Fluorescence and Luminescence Probes for Biological Activity, W.T. Mason (ed.), San Diego: Academic Press, 1993; Receptor-Ligand Interaction. A Practical Approach, E.C. Hulme (ed.), Oxford: IRL Press, 1992, each of which is hereby incorporated by reference in their entireties.

General Administration and Pharmaceutical Compositions

When used as pharmaceuticals, the compounds of the invention are typically administered in the form of a pharmaceutical composition. Such compositions can be prepared using procedures well known in the pharmaceutical art and comprise at least one compound of the invention. The compounds of the invention may also be administered alone or in combination with adjuvants that enhance stability of the compounds of the invention, facilitate

administration of pharmaceutical compositions containing them in certain embodiments, provide increased dissolution or dispersion, increased inhibitory activity, provide adjunct therapy, and the like. The compounds according to the invention may be used on their own or in conjunction with other active substances according to the invention, optionally also in conjunction with other pharmacologically active substances. In general, the compounds of this invention are administered in a therapeutically or pharmaceutically effective amount, but may be administered in lower amounts for diagnostic or other purposes.

In particular, the compounds of the invention are useful in combination with glucocorticoids or corticosteroids. As pointed out above, standard therapy for a variety of immune and inflammatory disorders includes administration of corticosteroids, which have the ability to suppress immunologic and inflammatory responses. (A.P. Truhan *et al.*, Annals of Allergy, 1989, 62, pp. 375-391; J.D. Baxter, Hospital Practice, 1992, 27, pp. 111-134; R.P. Kimberly, Curr. Opin. Rheumatol., 1992, 4, pp. 325-331; M.H. Weisman, Curr. Opin. Rheumatol., 1995, 7, pp. 183-190; W. Sterry, Arch. Dermatol. Res., 1992, 284 (Suppl.), pp. S27-S29). While therapeutically beneficial, however, the use of corticosteroids is associated with a number of side effects, ranging from mild to possibly life threatening, especially with prolonged and/or high dose steroid usage. Accordingly, methods and compositions that enable the use of a lower effective dosage of corticosteroids (referred to as the "steroid sparing effect") would be highly desirable to avoid unwanted side effects. The compounds of the invention provide such a steroid sparing effect by achieving the desired therapeutic effect while allowing the use of lower doses and less frequent administration of glucocorticoids or corticosteroids.

Administration of the compounds of the invention, in pure form or in an appropriate pharmaceutical composition, can be carried out using any of the accepted modes of administration of pharmaceutical compositions. Thus, administration can be, for example, orally, buccally (e.g., sublingually), nasally, parenterally, topically, transdermally, vaginally, or rectally, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as, for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages. The pharmaceutical compositions will generally include a conventional pharmaceutical carrier or excipient and a compound of the invention as

the/an active agent, and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, diluents, vehicles, or combinations thereof. Such pharmaceutically acceptable excipients, carriers, or additives as well as methods of making pharmaceutical compositions for various modes or administration are well-known to those of skill in the art. The state of the art is evidenced, e.g., by Remington: The Science and Practice of Pharmacy, 20th Edition, A. Gennaro (ed.), Lippincott Williams & Wilkins, 2000; Handbook of Pharmaceutical Additives, Michael & Irene Ash (eds.), Gower, 1995; Handbook of Pharmaceutical Excipients, A.H. Kibbe (ed.), American Pharmaceutical Ass'n, 2000; H.C. Ansel and N.G. Popovish, Pharmaceutical Dosage Forms and Drug Delivery Systems, 5th ed., Lea and Febiger, 1990; each of which is incorporated herein by reference in their entireties to better describe the state of the art.

As one of skill in the art would expect, the forms of the compounds of the invention utilized in a particular pharmaceutical formulation will be selected (e.g., salts) that possess suitable physical characteristics (e.g., water solubility) that is required for the formulation to be efficacious.

Pharmaceutical compositions suitable for buccal (sub-lingual) administration include lozenges comprising a compound of the present invention in a flavored base, usually sucrose, and acacia or tragacanth, and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

Pharmaceutical compositions suitable for parenteral administration comprise sterile aqueous preparations of a compound of the present invention. These preparations are preferably administered intravenously, although administration can also be effected by means of subcutaneous, intramuscular, or intradermal injection. Injectable pharmaceutical formulations are commonly based upon injectable sterile saline, phosphate-buffered saline, oleaginous suspensions, or other injectable carriers known in the art and are generally rendered sterile and isotonic with the blood. The injectable pharmaceutical formulations may therefore be provided as a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, including 1,3-butanediol, water, Ringer's solution, isotonic sodium chloride solution, fixed oils such as synthetic mono- or diglycerides, fatty acids such as oleic acid, and the like.

Such injectable pharmaceutical formulations are formulated according to the known art using suitable dispersing or setting agents and suspending agents. Injectable compositions will generally contain from 0.1 to 5% w/w of a compound of the invention.

Solid dosage forms for oral administration of the compounds include capsules, tablets, pills, powders, and granules. For such oral administration, a pharmaceutically acceptable composition containing a compound(s) of the invention is formed by the incorporation of any of the normally employed excipients, such as, for example, pharmaceutical grades of mannitol, lactose, starch, pregelatinized starch, magnesium stearate, sodium saccharine, talcum, cellulose ether derivatives, glucose, gelatin, sucrose, citrate, propyl gallate, and the like. Such solid pharmaceutical formulations may include formulations, as are well-known in the art, to provide prolonged or sustained delivery of the drug to the gastrointestinal tract by any number of mechanisms, which include, but are not limited to, pH sensitive release from the dosage form based on the changing pH of the small intestine, slow erosion of a tablet or capsule, retention in the stomach based on the physical properties of the formulation, bioadhesion of the dosage form to the mucosal lining of the intestinal tract, or enzymatic release of the active drug from the dosage form.

Liquid dosage forms for oral administration of the compounds include emulsions, microemulsions, solutions, suspensions, syrups, and elixirs, optionally containing pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like. These compositions can also contain additional adjuvants such as wetting, emulsifying, suspending, sweetening, flavoring, and perfuming agents.

Topical dosage forms of the compounds include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants, eye ointments, eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams. Topical application may be once or more than once per day depending upon the usual medical considerations. Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles. The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol

for lotions. Such carriers may be present as from about 1% up to about 98% of the formulation, more usually they will form up to about 80% of the formulation.

Transdermal administration is also possible. Pharmaceutical compositions suitable for transdermal administration can be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen. Such patches suitably contain a compound of the invention in an optionally buffered, aqueous solution, dissolved and/or dispersed in an adhesive, or dispersed in a polymer. A suitable concentration of the active compound is about 1% to 35%, preferably about 3% to 15%.

For administration by inhalation, the compounds of the invention are conveniently delivered in the form of an aerosol spray from a pump spray device not requiring a propellant gas or from a pressurized pack or a nebulizer with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, tetrafluoroethane, heptafluoropropane, carbon dioxide, or other suitable gas. In any case, the aerosol spray dosage unit may be determined by providing a valve to deliver a metered amount so that the resulting metered dose inhaler (MDI) is used to administer the compounds of the invention in a reproducible and controlled way. Such inhaler, nebulizer, or atomizer devices are known in the prior art, for example, in PCT International Publication Nos. WO 97/12687 (particularly Figure 6 thereof, which is the basis for the commercial RESPIMAT® nebulizer); WO 94/07607; WO 97/12683; and WO 97/20590, to which reference is hereby made and each of which is incorporated herein by reference in their entireties.

Rectal administration can be effected utilizing unit dose suppositories in which the compound is admixed with low-melting water-soluble or insoluble solids such as fats, cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights, or fatty acid esters of polyethylene glycols, or the like. The active compound is usually a minor component, often from about 0.05 to 10% by weight, with the remainder being the base component.

In all of the above pharmaceutical compositions, the compounds of the invention are formulated with an acceptable carrier or excipient. The carriers or excipients used must, of course, be acceptable in the sense of being compatible with the other ingredients of the composition and must not be deleterious to the patient. The carrier or excipient can be a solid or a liquid, or both, and is preferably formulated with the compound of the invention as a unit-dose composition, for example, a tablet, which can contain from 0.05% to 95% by weight of the active compound. Such carriers or excipients include inert fillers or diluents, binders, lubricants, disintegrating agents, solution retardants, resorption accelerators, absorption agents, and coloring agents. Suitable binders include starch, gelatin, natural sugars such as glucose or β-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

Generally, a therapeutically effective daily dose is from about 0.001 mg to about 15 mg/kg of body weight per day of a compound of the invention; preferably, from about 0.1 mg to about 10 mg/kg of body weight per day; and most preferably, from about 0.1 mg to about 1.5 mg/kg of body weight per day. For example, for administration to a 70 kg person, the dosage range would be from about 0.07 mg to about 1050 mg per day of a compound of the invention, preferably from about 7.0 mg to about 700 mg per day, and most preferably from about 7.0 mg to about 105 mg per day. Some degree of routine dose optimization may be required to determine an optimal dosing level and pattern.

Pharmaceutically acceptable carriers and excipients encompass all the foregoing additives and the like.

Examples of Pharmaceutical Formulations

A. TABLETS	
Component	**Amount per tablet (mg)**
active substance	100
lactose	140
corn starch	240
polyvinylpyrrolidone	15
magnesium stearate	5
TOTAL	500

The finely ground active substance, lactose, and some of the corn starch are mixed together. The mixture is screened, then moistened with a solution of polyvinylpyrrolidone in water, kneaded, wet-granulated and dried. The granules, the remaining corn starch and the magnesium stearate are screened and mixed together. The mixture is compressed to produce tablets of suitable shape and size.

B. TABLETS	
Component	**Amount per tablet (mg)**
active substance	80
lactose	55
corn starch	190
polyvinylpyrrolidone	15
magnesium stearate	2
microcrystalline cellulose	35
sodium-carboxymethyl starch	23
TOTAL	400

The finely ground active substance, some of the corn starch, lactose, microcrystalline cellulose, and polyvinylpyrrolidone are mixed together, the mixture is screened and worked with the remaining corn starch and water to form a granulate which is dried and screened. The sodium-

carboxymethyl starch and the magnesium stearate are added and mixed in and the mixture is compressed to form tablets of a suitable size.

C. COATED TABLETS	
Component	**Amount per tablet (mg)**
active substance	5
lactose	30
corn starch	41.5
polyvinylpyrrolidone	3
magnesium stearate	0.5
TOTAL	90

The active substance, corn starch, lactose, and polyvinylpyrrolidone are thoroughly mixed and moistened with water. The moist mass is pushed through a screen with a 1 mm mesh size, dried at about 45°C and the granules are then passed through the same screen. After the magnesium stearate has been mixed in, convex tablet cores with a diameter of 6 mm are compressed in a tablet-making machine. The tablet cores thus produced are coated in known manner with a covering consisting essentially of sugar and talc. The finished coated tablets are polished with wax.

D. CAPSULES	
Component	**Amount per capsule (mg)**
active substance	50
corn starch	268.5
magnesium stearate	1.5
TOTAL	320

The substance and corn starch are mixed and moistened with water. The moist mass is screened and dried. The dry granules are screened and mixed with magnesium stearate. The finished mixture is packed into size 1 hard gelatine capsules.

E. AMPOULE SOLUTION	
Component	**Amount per ampoule**
active substance	50 mg
sodium chloride	50 mg
water for inj.	5 mL

The active substance is dissolved in water at its own pH or optionally at pH 5.5 to 6.5 and sodium chloride is added to make it isotonic. The solution obtained is filtered free from pyrogens and the filtrate is transferred under aseptic conditions into ampoules which are then sterilized and sealed by fusion. The ampoules contain 5 mg, 25 mg, and 50 mg of active substance.

F. SUPPOSITORIES	
Component	**Amount per suppository (mg)**
active substance	50
solid fat	1650
TOTAL	1700

The hard fat is melted. At 40°C, the ground active substance is homogeneously dispersed therein. The mixture is cooled to 38°C and poured into slightly chilled suppository molds.

G. METERING AEROSOL	
Component	**Amount**
active substance	0.005
sorbitan trioleate	0.1
monofluorotrichloromethane and difluorodichloromethane (2:3)	to 100

The suspension is transferred into a conventional aerosol container with a metering valve. Preferably, 50 μL of suspension are delivered per spray. The active substance may also be metered in higher doses if desired (e.g., 0.02% by weight).

H. POWDER FOR INHALATION	
Component	**Amount**
active substance	1.0 mg
lactose monohydrate	to 25 mg

I. POWDER FOR INHALATION	
Component	**Amount**
active substance	2.0 mg
lactose monohydrate	to 25 mg

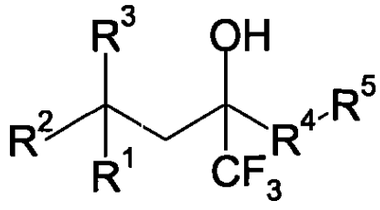
J. POWDER FOR INHALATION	
Component	**Amount**
active substance	1.0 mg
lactose monohydrate	to 5 mg

K. POWDER FOR INHALATION	
Component	**Amount**
active substance	2.0 mg
lactose monohydrate	to 5 mg

In Examples H, I, J, and K, the powder for inhalation is produced in the usual way by mixing the individual ingredients together.

We claim:

1. A compound of Formula (IA)



(IA)

wherein:

R^1 is an aryl or heteroaryl group, each optionally independently substituted with one to three substituent groups,

wherein each substituent group of R^1 is independently C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, C_3-C_8 cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_5 alkoxy, C_2-C_5 alkenyloxy, C_2-C_5 alkynyloxy, aryloxy, acyl, C_1-C_5 alkoxycarbonyl, C_1-C_5 alkanoyloxy, C_1-C_5 alkanoyl, aroyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, aminocarbonyloxy, C_1-C_5 alkylaminocarbonyloxy, C_1-C_5 dialkylaminocarbonyloxy, C_1-C_5 alkanoylamino, C_1-C_5 alkoxycarbonylamino, C_1-C_5 alkylsulfonylamino, aminosulfonyl, C_1-C_5 alkylaminosulfonyl, C_1-C_5 dialkylaminosulfonyl, halogen, hydroxy, carboxy, cyano, trifluoromethyl, trifluoromethoxy, nitro, or amino wherein the nitrogen atom is optionally independently mono- or di-substituted by C_1-C_5 alkyl or aryl; or ureido wherein either nitrogen atom is optionally independently substituted with C_1-C_5 alkyl; or C_1-C_5 alkylthio wherein the sulfur atom is optionally oxidized to a sulfoxide or sulfone,

wherein each substituent group of R^1 is optionally independently substituted with one to three substituent groups selected from methyl, methoxy, halogen, hydroxy, oxo, cyano, or amino,

R^2 and R^3 are each independently hydrogen or C_1-C_5 alkyl, or R^2 and R^3 together with the carbon atom they are commonly attached to form a C_3-C_8 spiro cycloalkyl ring;

R^4 is C_1-C_5 alkyl, C_2-C_5 alkenyl, or C_2-C_5 alkynyl, each optionally independently substituted with one to three substituent groups,

wherein each substituent group of R^4 is independently C_1-C_3 alkyl, hydroxy, halogen, amino, or oxo; and

R^5 is a heteroaryl group optionally independently substituted with one to three substituent groups,

wherein each substituent group of R^5 is independently C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, C_3-C_8 cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_5 alkoxy, C_2-C_5 alkenyloxy, C_2-C_5 alkynyloxy, aryloxy, acyl, C_1-C_5 alkoxycarbonyl, C_1-C_5 alkanoyloxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, aminocarbonyloxy, C_1-C_5 alkylaminocarbonyloxy, C_1-C_5 dialkylaminocarbonyloxy, C_1-C_5 alkanoylamino, C_1-C_5 alkoxycarbonylamino, C_1-C_5 alkylsulfonylamino, aminosulfonyl, C_1-C_5 alkylaminosulfonyl, C_1-C_5 dialkylaminosulfonyl, halogen, hydroxy, carboxy, cyano, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, nitro, or amino wherein the nitrogen atom is optionally independently mono- or di-substituted by C_1-C_5 alkyl; or ureido wherein either nitrogen atom is optionally independently substituted with C_1-C_5 alkyl; or C_1-C_5 alkylthio wherein the sulfur atom is optionally oxidized to a sulfoxide or sulfone,

wherein each substituent group of R^5 is optionally independently substituted with one to three substituent groups selected from C_1-C_3 alkyl, C_1-C_3 alkoxy, halogen, hydroxy, oxo, cyano, amino, or trifluoromethyl,

or a tautomer, prodrug, solvate, or salt thereof.

2. The compound of Formula (IA) according to claim 1, wherein:

R^1 is thienyl, phenyl, naphthyl, dihydrobenzofuranyl, benzofuranyl, chromanyl, dihydroindolyl, indolyl, dihydrobenzothienyl, benzothienyl, benzodioxolanyl,

dihydrobenzoxazolyl, benzoxazolyl, benzisoxazolyl, benzpyrazolyl, benzimidazolyl, quinolinyl, pyridinyl, pyrimidinyl, or pyrazinyl, each optionally independently substituted with one to three substituent groups,

wherein each substituent group of R^1 is independently C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, C_1-C_3 alkoxy, C_2-C_3 alkenyloxy, C_1-C_3 alkanoyl, C_1-C_3 alkoxycarbonyl, C_1-C_3 alkanoyloxy, halogen, hydroxy, carboxy, cyano, trifluoromethyl, trifluoromethoxy, nitro, or C_1-C_3 alkylthio wherein the sulfur atom is optionally oxidized to a sulfoxide or sulfone,

wherein each substituent group of R^1 is optionally independently substituted with a substituent group selected from methyl, methoxy, halogen, hydroxy, oxo, cyano, or amino;

R^2 and R^3 are each independently hydrogen or C_1-C_3 alkyl, or R^2 and R^3 together with the carbon atom they are commonly attached to form a C_3-C_6 spiro cycloalkyl ring;

R^4 is CH_2; and

R^5 is an imidazolyl, pyridyl, indolyl, azaindolyl, diazaindolyl, benzofuranyl, furanopyridinyl, furanopyrimidinyl, benzothienyl, thienopyridinyl, thienopyrimidinyl, benzoxazolyl, oxazolopyridinyl, benzothiazolyl, thiazolopyridinyl, benzimidazolyl, imidazolopyridinyl, quinolinyl, or isoquinolinyl group, each optionally independently substituted with one to three substituent groups,

wherein each substituent group of R^5 is independently C_1-C_3 alkyl, C_2-C_3 alkenyl, phenyl, C_1-C_3 alkoxy, methoxycarbonyl, aminocarbonyl, C_1-C_3 alkylaminocarbonyl, C_1-C_3 dialkylaminocarbonyl, heterocyclylcarbonyl, fluoro, chloro, bromo, oxo, cyano, trifluoromethyl, or C_1-C_3 alkylthio wherein the sulfur atom is optionally oxidized to a sulfoxide or sulfone,

wherein each substituent group of R^5 is optionally independently substituted with a substituent group selected from methyl, methoxy, fluoro, chloro, bromo, or trifluoromethyl,

or a tautomer, prodrug, solvate, or salt thereof.

3. The compound of Formula (IA) according to claim 1, wherein:

R^1 is phenyl, naphthyl, pyridyl, chromanyl, dihydrobenzofuranyl, or benzofuranyl, each optionally independently substituted with one or two substituent groups,

wherein each substituent group of R^1 is independently methyl, ethyl, methoxy, ethoxy, fluoro, chloro, bromo, hydroxy, trifluoromethyl, trifluoromethoxy, or cyano;

R^2 and R^3 are each independently methyl, or R^2 and R^3 together with the carbon atom they are commonly attached to form a spiro cyclopropyl ring;

R^4 is CH_2; and

R^5 is a pyridyl, indolyl, azaindolyl, benzofuranyl, furanopyridinyl, thienopyridinyl, benzoxazolyl, benzimidazolyl, quinolinyl, or isoquinolinyl group, each optionally independently substituted with one to three substituent groups,

wherein each substituent group of R^5 is independently methyl, phenyl, methoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, morpholinylcarbonyl, fluoro, chloro, bromo, cyano, or trifluoromethyl,

or a tautomer, prodrug, solvate, or salt thereof.

4. The compound of Formula (IA) according to claim 1, wherein:

R^1 is phenyl, dihydrobenzofuranyl, or benzofuranyl, each optionally independently substituted with one to three substituent groups,

wherein each substituent group of R^1 is independently C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, C_1-C_3 alkoxy, C_2-C_3 alkenyloxy, C_1-C_3 alkanoyl, C_1-C_3 alkoxycarbonyl, C_1-C_3 alkanoyloxy, halogen, hydroxy, carboxy, cyano, trifluoromethyl, nitro, or C_1-C_3 alkylthio wherein the sulfur atom is optionally oxidized to a sulfoxide or sulfone; and

R^2 and R^3 are each independently hydrogen or C_1-C_3 alkyl,

or a tautomer, prodrug, solvate, or salt thereof.

5. A compound selected from:

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(4,6-dimethylpyridin-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(pyridin-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(6-methylpyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(4-methylpyridin-2-ylmethyl)pentan-2-ol;

4-Fluoro-2-(4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-pyridin-2-ylmethylbutyl)phenol;

2-(4,5-Dimethylthiazol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

2-(4,5-Dimethyloxazol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(3-methylpyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(5-methylpyridin-2-ylmethyl)pentan-2-ol;

2-Benzothiazol-2-ylmethyl-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(5-phenylbenzoxazol-2-ylmethyl)pentan-2-ol;

2-Benzofuran-2-ylmethyl-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(3-methylbenzofuran-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-thiophen-2-ylmethylpentan-2-ol;

5-(5-Fluoro-2-methoxyphenyl)-5-methyl-2-pyridin-2-yl-3-trifluoromethylhexan-3-ol;

5-(5-Fluoro-2-methoxyphenyl)-5-methyl-2-pyridin-2-yl-3-trifluoromethylhexan-3-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(5-methylbenzooxazol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(5-methylbenzothiazol-2-ylmethyl)pentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(5-methylbenzooxazol-2-ylmethyl)butyl]phenol;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(5-methylbenzothiazol-2-ylmethyl)butyl]phenol;

1,1,1-Trifluoro-4-methyl-4-phenyl-2-pyridin-2-ylmethylpentan-2-ol;

2-(4,6-Dimethylpyridin-2-ylmethyl)-1,1,1-trifluoro-4-methyl-4-phenylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-pyrimidin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(4-methylquinolin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1-phenyl-1*H*-pyrazol-3-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1-methyl-1*H*-imidazol-2-ylmethyl)pentan-2-ol;

5-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-3-phenylisoxazole-4-carboxylic acid methylamide;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-pyrazin-2-ylmethylpentan-2-ol;
4-(2-Allyloxy-5-fluorophenyl)-1,1,1-trifluoro-4-methyl-2-pyridin-2-ylmethylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(3-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

2-Benzooxazol-2-ylmethyl-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-pyridazin-3-ylmethylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-pyridin-3-ylmethylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(5-methylpyridin-3-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-quinolin-2-ylmethylpentan-2-ol;

4-(4-Chlorophenyl)-1,1,1-trifluoro-4-methyl-2-pyridin-2-ylmethylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(6-fluoropyridin-2-ylmethyl)-4-methylpentan-2-ol;

6-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]nicotinonitrile;

2-(1*H*-Indol-2-ylmethyl)-1,1,1-trifluoro-4-(4-fluorophenyl)-4-methylpentan-2-ol;

2-(6-Chloro-4-trifluoromethylpyridin-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

2-(5-Chloro-7-fluoro-1*H*-indol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

4-(3,4-Dichlorophenyl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-(2,6-Dichloropyridin-4-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-isoquinolin-1-ylmethyl-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-[3-(2,6-Dichloropyridin-4-ylmethyl)-4,4,4-trifluoro-3-hydroxy-1,1-dimethylbutyl]-4-fluorophenol;

4-Fluoro-2-(4,4,4-trifluoro-3-hydroxy-3-isoquinolin-1-ylmethyl-1,1-dimethylbutyl)phenol;

4-(5-Bromo-2,3-dihydrobenzofuran-7-yl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-pyridin-2-ylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(6-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

2-(1*H*-Benzimidazol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(6-fluoro-1*H*-indol-2-ylmethyl)-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorophenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(quinolin-4-ylmethyl)pentan-2-ol;

4-(2,3-dihydro-5-cyanobenzofuran-7-yl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(2-chloropyridin-4-ylmethyl)pentan-2-ol;

4-(3,4-Difluorophenyl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-hydroxyphenyl)-4-methyl-2-(2-chloropyridin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(2-chloropyridin-5-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(2-chloroquinolin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1-oxypyridin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-hydroxyphenyl)-4-methyl-2-(2-chloroquinolin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-(4-methoxyphenyl)-4-methylpentan-2-ol;

4-[4,4,4-Trifluoro-3-hydroxy-3-(1*H*-indol-2-ylmethyl)-1,1-dimethylbutyl]phenol;

1,1,1-Trifluoro-2-(5-fluoro-1*H*-indol-2-ylmethyl)-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(5-methyl-1*H*-indol-2-ylmethyl)-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

4-(2,3-dihydrobenzofuran-7-yl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-Benzimidazol-1-ylmethyl-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1-oxypyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-methylphenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(6-chlorobenzimidazol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(2-fluoropyridin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(2-bromopyridin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(7-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(4-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-methyl-4-quinolin-4-yl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(7-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(7-methyl-1*H*-benzoimidazol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(6-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-2-quinolin-4-ylmethyl-3-[1-(2-trifluoromethoxyphenyl)cyclopropyl]propan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(6-trifluoromethyl-1*H*-benzoimidazol-2-ylmethyl)pentan-2-ol;

2-(5-Chloro-6-fluoro-1*H*-benzoimidazol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-3-[1-(5-fluoro-2-methoxyphenyl)cyclopropyl]-2-(1*H*-indol-2-ylmethyl)propan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(4-methyl-1*H*-indol-2-ylmethyl)butyl]phenol;

4-Fluoro-2-[4,4,4-trifluoro-3-(7-fluoro-1*H*-indol-2-ylmethyl)-3-hydroxy-1,1-dimethylbutyl]phenol;

1,1,1-Trifluoro-2-(6-fluoro-1*H*-benzoimidazol-2-ylmethyl)-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

2-(6,7-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(5-Bromo-2,3-dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(3-Ethyl-2-methoxyphenyl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

3-[1-(2,5-Difluorophenyl)cyclopropyl]-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)propan-2-ol;

1,1,1-Trifluoro-3-[1-(4-fluorophenyl)cyclopropyl]-2-(1*H*-indol-2-ylmethyl)propan-2-ol;

2-Ethyl-6-(4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(6-fluoro-4-methyl-1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-(4,6-Dimethyl-1*H*-indol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

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4-(3-Ethyl-2-methoxyphenyl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-Ethyl-6-[4,4,4-trifluoro-3-hydroxy-3-(1*H*-indol-2-ylmethyl)-1,1-dimethylbutyl]phenol;

2-[3-(6,7-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-4,4,4-trifluoro-3-hydroxy-1,1-dimethylbutyl]-4-fluorophenol;

2-(7-Chloro-5-trifluoromethyl-1*H*-benzoimidazol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

2-(5,7-Dimethyl-1*H*-benzoimidazol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-(5-fluoro-2-methylphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-(4-fluorophenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-(3-fluorophenyl)-4-methylpentan-2-ol;

2-[3-(5,7-Dimethyl-1*H*-benzoimidazol-2-ylmethyl)-4,4,4-trifluoro-3-hydroxy-1,1-dimethylbutyl]-4-fluorophenol;

1,1,1-Trifluoro-4-(3-methoxyphenyl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-(3-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-4-methyl-2-(4-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-4-methyl-2-(4-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorophenyl)-4-methyl-2-(4-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-methyl-2-quinolin-4-ylmethyl-4-(3-trifluoromethylphenyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-4-methyl-2-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-4-methyl-2-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorophenyl)-4-methyl-2-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-4-methyl-2-(7-methyl-1*H*-benzoimidazol-2-ylmethyl)pentan-2-ol;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-3*H*-benzoimidazole-5-carbonitrile;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-(3-trifluoromethylphenyl)pentan-2-ol;

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1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

5-Fluoro-2-(4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)butyl]phenol;

4-(5-Bromo-4-fluoro-2-methoxyphenyl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

2-(6-Chloro-4-methyl-1*H*-indol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

2-(2-Phenyl-4-methylimidazol-1-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihydrobenzofuran-7-yl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

2-(2-Phenylimidazol-1-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihydrobenzofuran-7-yl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-methyl-4-(5-methyl-2,3-dihydrobenzofuran-7-yl)-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-phenylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-(5-methyl-2,3-dihydrobenzofuran-7-yl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(7-fluoro-4-methyl-1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-*m*-tolylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-naphthalen-2-ylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-*o*-tolylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-*p*-tolylpentan-2-ol;

4-(2,3-Dihydrobenzofuran-5-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(7-Bromo-2,3-dihydrobenzofuran-5-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(2,3-Dihydrobenzofuran-5-yl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(1-methoxynaphthalen-2-yl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

2-(4,4,4-Trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)naphthalen-1-ol;

1,1,1-Trifluoro-4-methyl-4-naphthalen-2-yl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-7-carbonitrile;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-(1-methoxynaphthalen-2-yl)-4-methylpentan-2-ol;

2-[4,4,4-Trifluoro-3-hydroxy-3-(1*H*-indol-2-ylmethyl)-1,1-dimethylbutyl]naphthalen-1-ol;

1,1,1-Trifluoro-4-methyl-2-quinolin-4-ylmethyl-4-*p*-tolylpentan-2-ol;

4-Chroman-8-yl-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-4-methyl-4-phenyl-2-quinolin-4-ylmethylpentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)butyl]phenol;

4-(6-Bromochroman-8-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)butyl]phenol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*b*]pyridin-2-ylmethyl)pentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[3,2-*b*]pyridin-2-ylmethyl)butyl]phenol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*b*]pyridin-2-ylmethyl)pentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[2,3-*b*]pyridin-2-ylmethyl)butyl]phenol;

1,1,1-Trifluoro-4-(3-fluorophenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-methyl-4-phenyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(7-fluoroquinolin-4-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-2-(7-fluoroquinolin-4-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-2-(5-fluoroquinolin-4-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-4-methylquinolin-8-yl)-4-(4-fluorophenyl)-4-methylpentan-2-ol;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

2-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

2-[4-(5-Fluoro-2-methylphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

1,1,1-Trifluoro-4-(2-methoxyphenyl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-(2-methoxyphenyl)-4-methylpentan-2-ol;

2-[4-(5-Fluoro-2,3-dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

4-(5-Bromo-2-methoxyphenyl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(5-Bromo-2-methoxyphenyl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-(4,4,4-Trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

1,1,1-Trifluoro-4-methyl-4-phenyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-[4-(5-Bromo-2,3-dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

4-Bromo-2-(4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

2-[4-(4-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

2-(2-Hydroxy-4-methyl-4-phenyl-2-trifluoromethylpentyl)-4-methyl-1*H*-indole-6-carbonitrile;

2-[4-(3-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

2-[4-(4-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

2-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-methyl-4-phenyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-(2-Hydroxy-4-methyl-4-phenyl-2-trifluoromethylpentyl)-1*H*-indole-5-carbonitrile;

2-[4-(3-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

2-[4-(4-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-(5,6,7,8-tetrahydroquinolin-4-ylmethyl)pentan-2-ol;

1-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-(2-Hydroxy-4-methyl-4-phenyl-2-trifluoromethylpentyl)-1*H*-indole-3-carbonitrile;

5-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)butyl]phenol;

2-[4-(4-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(3-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(4-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(5-Fluoro-2-methylphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-(4-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-methyl-4-phenylpentan-2-ol;

2-[4-(4-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carboxylic acid methyl ester;

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1-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(3-methyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(3-methoxyphenyl)-4-methyl-2-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

5-Fluoro-2-[4,4,4-trifluoro-3-(7-fluoro-1*H*-indol-2-ylmethyl)-3-hydroxy-1,1-dimethylbutyl]phenol;

2-[2-Hydroxy-4-(3-methoxyphenyl)-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(5-Fluoro-2-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(3-methyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)butyl]phenol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-thiophen-3-ylpentan-2-ol;

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1,1,1-Trifluoro-4-methyl-2-quinolin-4-ylmethyl-4-thiophen-3-ylpentan-2-ol;

5-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)butyl]phenol;

1,1,1-Trifluoro-4-(3-fluorophenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-[4-(4-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

3-(4,4,4-Trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(4-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

4-(5-Bromo-2-methoxyphenyl)-1,1,1-trifluoro-4-methyl-2-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

2-[4-(5-Bromo-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(5-Bromo-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carboxylic acid methyl ester;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carboxylic acid methyl ester;

4-(2,6-Dimethylphenyl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

3-[4,4,4-Trifluoro-3-hydroxy-3-(1*H*-indol-2-ylmethyl)-1,1-dimethylbutyl]phenol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihydrobenzofuran-7-yl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carboxylic acid methyl ester;

2-[2-Hydroxy-4-(3-methoxyphenyl)-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

2-[4-(5-Bromo-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

2-[4-(4-Fluoro-2-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(5-nitro-1*H*-indol-2-ylmethyl)pentan-2-ol;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carboxylic acid amide;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carboxylic acid dimethylamide;

{2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indol-5-yl}morpholin-4-ylmethanone;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-6-carboxylic acid methyl ester;

2-[4-(5-Fluoro-2-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-6-carboxylic acid methyl ester;

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2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-6-carboxylic acid; and

2-[4-(5-Fluoro-2-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-6-carboxylic acid,

or a tautomer, prodrug, solvate, or salt thereof.

6. A compound according to claim 5, the compound selected from:

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(pyridin-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(5-phenylbenzoxazol-2-ylmethyl)pentan-2-ol;

2-Benzofuran-2-ylmethyl-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(3-methylbenzofuran-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(3-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

6-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]nicotinonitrile;

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2-(1*H*-Indol-2-ylmethyl)-1,1,1-trifluoro-4-(4-fluorophenyl)-4-methylpentan-2-ol;

2-(6-Chloro-4-trifluoromethylpyridin-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

2-(5-Chloro-7-fluoro-1*H*-indol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

4-(3,4-Dichlorophenyl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-(2,6-Dichloropyridin-4-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-[3-(2,6-Dichloropyridin-4-ylmethyl)-4,4,4-trifluoro-3-hydroxy-1,1-dimethylbutyl]-4-fluorophenol;

4-Fluoro-2-(4,4,4-trifluoro-3-hydroxy-3-isoquinolin-1-ylmethyl-1,1-dimethylbutyl)phenol;

4-(5-Bromo-2,3-dihydrobenzofuran-7-yl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-pyridin-2-ylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(6-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

2-(1*H*-Benzimidazol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(6-fluoro-1*H*-indol-2-ylmethyl)-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorophenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(quinolin-4-ylmethyl)pentan-2-ol;

4-(2,3-dihydro-5-cyanobenzofuran-7-yl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(2-chloropyridin-4-ylmethyl)pentan-2-ol;

4-(3,4-Difluorophenyl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-hydroxyphenyl)-4-methyl-2-(2-chloropyridin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(2-chloroquinolin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-hydroxyphenyl)-4-methyl-2-(2-chloroquinolin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-(4-methoxyphenyl)-4-methylpentan-2-ol;

4-[4,4,4-Trifluoro-3-hydroxy-3-(1*H*-indol-2-ylmethyl)-1,1-dimethylbutyl]phenol;

1,1,1-Trifluoro-2-(5-fluoro-1*H*-indol-2-ylmethyl)-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(5-methyl-1*H*-indol-2-ylmethyl)-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

4-(2,3-dihydrobenzofuran-7-yl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-Benzimidazol-1-ylmethyl-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-methylphenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(6-chlorobenzimidazol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(2-fluoropyridin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(2-bromopyridin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(7-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(4-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(7-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(7-methyl-1*H*-benzoimidazol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(6-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(6-trifluoromethyl-1*H*-benzoimidazol-2-ylmethyl)pentan-2-ol;

2-(5-Chloro-6-fluoro-1*H*-benzoimidazol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-3-[1-(5-fluoro-2-methoxyphenyl)cyclopropyl]-2-(1*H*-indol-2-ylmethyl)propan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(4-methyl-1*H*-indol-2-ylmethyl)butyl]phenol;

4-Fluoro-2-[4,4,4-trifluoro-3-(7-fluoro-1*H*-indol-2-ylmethyl)-3-hydroxy-1,1-dimethylbutyl]phenol;

1,1,1-Trifluoro-2-(6-fluoro-1*H*-benzoimidazol-2-ylmethyl)-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

2-(6,7-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(5-Bromo-2,3-dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(3-Ethyl-2-methoxyphenyl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-3-[1-(4-fluorophenyl)cyclopropyl]-2-(1*H*-indol-2-ylmethyl)propan-2-ol;

2-Ethyl-6-(4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(6-fluoro-4-methyl-1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-(4,6-Dimethyl-1*H*-indol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

4-(3-Ethyl-2-methoxyphenyl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-Ethyl-6-[4,4,4-trifluoro-3-hydroxy-3-(1*H*-indol-2-ylmethyl)-1,1-dimethylbutyl]phenol;

2-[3-(6,7-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-4,4,4-trifluoro-3-hydroxy-1,1-dimethylbutyl]-4-fluorophenol;

2-(7-Chloro-5-trifluoromethyl-1*H*-benzoimidazol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

2-(5,7-Dimethyl-1*H*-benzoimidazol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-(5-fluoro-2-methylphenyl)-4-methylpentan-2-ol;

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1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-(4-fluorophenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-(3-fluorophenyl)-4-methylpentan-2-ol;

2-[3-(5,7-Dimethyl-1*H*-benzoimidazol-2-ylmethyl)-4,4,4-trifluoro-3-hydroxy-1,1-dimethylbutyl]-4-fluorophenol;

1,1,1-Trifluoro-4-(3-methoxyphenyl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-(3-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-4-methyl-2-(4-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-4-methyl-2-(4-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorophenyl)-4-methyl-2-(4-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-methyl-2-quinolin-4-ylmethyl-4-(3-trifluoromethylphenyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-4-methyl-2-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-4-methyl-2-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorophenyl)-4-methyl-2-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-4-methyl-2-(7-methyl-1*H*-benzoimidazol-2-ylmethyl)pentan-2-ol;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-3*H*-benzoimidazole-5-carbonitrile;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-(3-trifluoromethylphenyl)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

5-Fluoro-2-(4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)butyl]phenol;

4-(5-Bromo-4-fluoro-2-methoxyphenyl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

2-(6-Chloro-4-methyl-1*H*-indol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

2-(2-Phenyl-4-methylimidazol-1-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihydrobenzofuran-7-yl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

2-(2-Phenylimidazol-1-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihydrobenzofuran-7-yl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-methyl-4-(5-methyl-2,3-dihydrobenzofuran-7-yl)-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-phenylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-(5-methyl-2,3-dihydrobenzofuran-7-yl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(7-fluoro-4-methyl-1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-*m*-tolylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-naphthalen-2-ylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-*o*-tolylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-*p*-tolylpentan-2-ol;

4-(2,3-Dihydrobenzofuran-5-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(7-Bromo-2,3-dihydrobenzofuran-5-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(2,3-Dihydrobenzofuran-5-yl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(1-methoxynaphthalen-2-yl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

2-(4,4,4-Trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)naphthalen-1-ol;

1,1,1-Trifluoro-4-methyl-4-naphthalen-2-yl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-7-carbonitrile;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-(1-methoxynaphthalen-2-yl)-4-methylpentan-2-ol;

2-[4,4,4-Trifluoro-3-hydroxy-3-(1*H*-indol-2-ylmethyl)-1,1-dimethylbutyl]naphthalen-1-ol;

1,1,1-Trifluoro-4-methyl-2-quinolin-4-ylmethyl-4-*p*-tolylpentan-2-ol;

4-Chroman-8-yl-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-4-methyl-4-phenyl-2-quinolin-4-ylmethylpentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)butyl]phenol;

4-(6-Bromochroman-8-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)butyl]phenol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*b*]pyridin-2-ylmethyl)pentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[3,2-*b*]pyridin-2-ylmethyl)butyl]phenol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*b*]pyridin-2-ylmethyl)pentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[2,3-*b*]pyridin-2-ylmethyl)butyl]phenol;

1,1,1-Trifluoro-4-(3-fluorophenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-methyl-4-phenyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(7-fluoroquinolin-4-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-2-(7-fluoroquinolin-4-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-2-(5-fluoroquinolin-4-ylmethyl)-4-methylpentan-2-ol;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

2-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

2-[4-(5-Fluoro-2-methylphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

1,1,1-Trifluoro-4-(2-methoxyphenyl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-(2-methoxyphenyl)-4-methylpentan-2-ol;

2-[4-(5-Fluoro-2,3-dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

4-(5-Bromo-2-methoxyphenyl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(5-Bromo-2-methoxyphenyl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-(4,4,4-Trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

1,1,1-Trifluoro-4-methyl-4-phenyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-[4-(5-Bromo-2,3-dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

4-Bromo-2-(4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

2-[4-(4-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethyl-pentyl]-1*H*-indole-3-carbonitrile;

2-(2-Hydroxy-4-methyl-4-phenyl-2-trifluoromethylpentyl)-4-methyl-1*H*-indole-6-carbonitrile;

2-[4-(3-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

2-[4-(4-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

2-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-methyl-4-phenyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-(2-Hydroxy-4-methyl-4-phenyl-2-trifluoromethylpentyl)-1*H*-indole-5-carbonitrile;

2-[4-(3-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

2-[4-(4-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-(5,6,7,8-tetrahydroquinolin-4-ylmethyl)pentan-2-ol;

1-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-(2-Hydroxy-4-methyl-4-phenyl-2-trifluoromethylpentyl)-1*H*-indole-3-carbonitrile;

5-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)butyl]phenol;

2-[4-(4-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(3-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(4-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(5-Fluoro-2-methylphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-(4-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-methyl-4-phenylpentan-2-ol;

2-[4-(4-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carboxylic acid methyl ester;

1-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(3-methyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(3-methoxyphenyl)-4-methyl-2-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

2-[2-Hydroxy-4-(3-methoxyphenyl)-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

5-Fluoro-2-[4,4,4-trifluoro-3-(7-fluoro-1*H*-indol-2-ylmethyl)-3-hydroxy-1,1-dimethylbutyl]phenol;

2-[4-(5-Fluoro-2-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(3-methyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)butyl]phenol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-thiophen-3-ylpentan-2-ol;

1,1,1-Trifluoro-4-methyl-2-quinolin-4-ylmethyl-4-thiophen-3-ylpentan-2-ol;

5-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)butyl]phenol;

1,1,1-Trifluoro-4-(3-fluorophenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-[4-(4-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

3-(4,4,4-Trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(4-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

4-(5-Bromo-2-methoxyphenyl)-1,1,1-trifluoro-4-methyl-2-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

2-[4-(5-Bromo-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(5-Bromo-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carboxylic acid methyl ester;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carboxylic acid methyl ester;

4-(2,6-Dimethylphenyl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

3-[4,4,4-Trifluoro-3-hydroxy-3-(1*H*-indol-2-ylmethyl)-1,1-dimethylbutyl]phenol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihydrobenzofuran-7-yl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol; and

1-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carboxylic acid methyl ester,

or a tautomer, prodrug, solvate, or salt thereof.

7. A compound according to claim 6, the compound selected from:

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-(2,6-Dichloropyridin-4-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-[3-(2,6-Dichloropyridin-4-ylmethyl)-4,4,4-trifluoro-3-hydroxy-1,1-dimethylbutyl]-4-fluorophenol;

4-(5-Bromo-2,3-dihydrobenzofuran-7-yl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-(1*H*-Benzimidazol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorophenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(quinolin-4-ylmethyl)pentan-2-ol;

4-(2,3-dihydro-5-cyanobenzofuran-7-yl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(2-chloropyridin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-hydroxyphenyl)-4-methyl-2-(2-chloropyridin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(2-chloroquinolin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-hydroxyphenyl)-4-methyl-2-(2-chloroquinolin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-(4-methoxyphenyl)-4-methylpentan-2-ol;

4-[4,4,4-Trifluoro-3-hydroxy-3-(1*H*-indol-2-ylmethyl)-1,1-dimethylbutyl]phenol;

1,1,1-Trifluoro-2-(5-fluoro-1*H*-indol-2-ylmethyl)-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

4-(2,3-dihydrobenzofuran-7-yl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(2-bromopyridin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(7-methyl-1*H*-benzoimidazol-2-ylmethyl)pentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(4-methyl-1*H*-indol-2-ylmethyl)butyl]phenol;

4-Fluoro-2-[4,4,4-trifluoro-3-(7-fluoro-1*H*-indol-2-ylmethyl)-3-hydroxy-1,1-dimethylbutyl]phenol;

1,1,1-Trifluoro-2-(6-fluoro-1*H*-benzoimidazol-2-ylmethyl)-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

2-(6,7-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(5-Bromo-2,3-dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(3-Ethyl-2-methoxyphenyl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

2-Ethyl-6-(4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

2-Ethyl-6-[4,4,4-trifluoro-3-hydroxy-3-(1*H*-indol-2-ylmethyl)-1,1-dimethylbutyl]phenol;

2-(5,7-Dimethyl-1*H*-benzoimidazol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

2-[3-(5,7-Dimethyl-1*H*-benzoimidazol-2-ylmethyl)-4,4,4-trifluoro-3-hydroxy-1,1-dimethylbutyl]-4-fluorophenol;

1,1,1-Trifluoro-4-(3-methoxyphenyl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-(3-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-4-methyl-2-(4-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-4-methyl-2-(4-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorophenyl)-4-methyl-2-(4-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-methyl-2-quinolin-4-ylmethyl-4-(3-trifluoromethylphenyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-4-methyl-2-(7-methyl-1*H*-benzoimidazol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-(3-trifluoromethylphenyl)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

5-Fluoro-2-(4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

4-(5-Bromo-4-fluoro-2-methoxyphenyl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

2-(2-Phenyl-4-methylimidazol-1-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihydrobenzofuran-7-yl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

2-(2-Phenylimidazol-1-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihydrobenzofuran-7-yl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-methyl-4-(5-methyl-2,3-dihydrobenzofuran-7-yl)-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-phenylpentan-2-ol;

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1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-(5-methyl-2,3-dihydrobenzofuran-7-yl)pentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-*m*-tolylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-naphthalen-2-ylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-*o*-tolylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-*p*-tolylpentan-2-ol;

4-(2,3-Dihydrobenzofuran-5-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(7-Bromo-2,3-dihydrobenzofuran-5-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(2,3-Dihydrobenzofuran-5-yl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(1-methoxynaphthalen-2-yl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

2-(4,4,4-Trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)naphthalen-1-ol;

1,1,1-Trifluoro-4-methyl-4-naphthalen-2-yl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-(1-methoxynaphthalen-2-yl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-methyl-2-quinolin-4-ylmethyl-4-*p*-tolylpentan-2-ol;

4-Chroman-8-yl-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-4-methyl-4-phenyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(6-Bromochroman-8-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*b*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*b*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorophenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-methyl-4-phenyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(7-fluoroquinolin-4-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-2-(7-fluoroquinolin-4-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-2-(5-fluoroquinolin-4-ylmethyl)-4-methylpentan-2-ol;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

2-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

2-[4-(5-Fluoro-2-methylphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

1,1,1-Trifluoro-4-(2-methoxyphenyl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-(2-methoxyphenyl)-4-methylpentan-2-ol;

2-[4-(5-Fluoro-2,3-dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

4-(5-Bromo-2-methoxyphenyl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(5-Bromo-2-methoxyphenyl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-(4,4,4-Trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

1,1,1-Trifluoro-4-methyl-4-phenyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-[4-(5-Bromo-2,3-dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

4-Bromo-2-(4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-[4-(4-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethyl-pentyl]-1*H*-indole-3-carbonitrile;

2-(2-Hydroxy-4-methyl-4-phenyl-2-trifluoromethylpentyl)-4-methyl-1*H*-indole-6-carbonitrile;

2-[4-(3-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

2-[4-(4-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

2-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-methyl-4-phenyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-(2-Hydroxy-4-methyl-4-phenyl-2-trifluoromethylpentyl)-1*H*-indole-5-carbonitrile;

2-[4-(3-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

2-[4-(4-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-(5,6,7,8-tetrahydroquinolin-4-ylmethyl)pentan-2-ol;

1-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-(2-Hydroxy-4-methyl-4-phenyl-2-trifluoromethylpentyl)-1*H*-indole-3-carbonitrile;

5-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)butyl]phenol;

2-[4-(4-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(3-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(4-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(5-Fluoro-2-methylphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)butyl]phenol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-methyl-4-phenylpentan-2-ol;

2-[4-(4-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carboxylic acid methyl ester;

1-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(3-methyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(3-methoxyphenyl)-4-methyl-2-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

2-[2-Hydroxy-4-(3-methoxyphenyl)-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)butyl]phenol;

5-Fluoro-2-[4,4,4-trifluoro-3-(7-fluoro-1*H*-indol-2-ylmethyl)-3-hydroxy-1,1-dimethylbutyl]phenol;

2-[4-(5-Fluoro-2-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(3-methyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)butyl]phenol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-thiophen-3-ylpentan-2-ol;

1,1,1-Trifluoro-4-methyl-2-quinolin-4-ylmethyl-4-thiophen-3-ylpentan-2-ol;

5-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)butyl]phenol;

1,1,1-Trifluoro-4-(3-fluorophenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

3-(4,4,4-Trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

2-[4-(5-Bromo-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carboxylic acid methyl ester;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carboxylic acid methyl ester;

4-(2,6-Dimethylphenyl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

3-[4,4,4-Trifluoro-3-hydroxy-3-(1*H*-indol-2-ylmethyl)-1,1-dimethylbutyl]phenol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihydrobenzofuran-7-yl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-[2-Hydroxy-4-(3-methoxyphenyl)-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

2-[4-(5-Bromo-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

2-[4-(4-Fluoro-2-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(5-nitro-1*H*-indol-2-ylmethyl)pentan-2-ol;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carboxylic acid amide;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carboxylic acid dimethylamide;

{2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indol-5-yl}morpholin-4-ylmethanone;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-6-carboxylic acid methyl ester;

2-[4-(5-Fluoro-2-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-6-carboxylic acid methyl ester;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-6-carboxylic acid; and

2-[4-(5-Fluoro-2-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-6-carboxylic acid,

or a tautomer, prodrug, solvate, or salt thereof.

8. A compound selected from:

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-(2,6-Dichloropyridin-4-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-[3-(2,6-Dichloropyridin-4-ylmethyl)-4,4,4-trifluoro-3-hydroxy-1,1-dimethylbutyl]-4-fluorophenol;

4-(5-Bromo-2,3-dihydrobenzofuran-7-yl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-(1*H*-Benzimidazol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorophenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(quinolin-4-ylmethyl)pentan-2-ol;

4-(2,3-dihydro-5-cyanobenzofuran-7-yl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(2-chloropyridin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-hydroxyphenyl)-4-methyl-2-(2-chloropyridin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(2-chloroquinolin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-hydroxyphenyl)-4-methyl-2-(2-chloroquinolin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-(4-methoxyphenyl)-4-methylpentan-2-ol;

4-[4,4,4-Trifluoro-3-hydroxy-3-(1*H*-indol-2-ylmethyl)-1,1-dimethylbutyl]phenol;

1,1,1-Trifluoro-2-(5-fluoro-1*H*-indol-2-ylmethyl)-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

4-(2,3-dihydrobenzofuran-7-yl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(2-bromopyridin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(7-methyl-1*H*-benzoimidazol-2-ylmethyl)pentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(4-methyl-1*H*-indol-2-ylmethyl)butyl]phenol;

4-Fluoro-2-[4,4,4-trifluoro-3-(7-fluoro-1*H*-indol-2-ylmethyl)-3-hydroxy-1,1-dimethylbutyl]phenol;

1,1,1-Trifluoro-2-(6-fluoro-1*H*-benzoimidazol-2-ylmethyl)-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

2-(6,7-Difluoro-1*H*-benzoimidazol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(5-Bromo-2,3-dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(3-Ethyl-2-methoxyphenyl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

2-Ethyl-6-(4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

2-Ethyl-6-[4,4,4-trifluoro-3-hydroxy-3-(1*H*-indol-2-ylmethyl)-1,1-dimethylbutyl]phenol;

2-(5,7-Dimethyl-1*H*-benzoimidazol-2-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

2-[3-(5,7-Dimethyl-1*H*-benzoimidazol-2-ylmethyl)-4,4,4-trifluoro-3-hydroxy-1,1-dimethylbutyl]-4-fluorophenol;

1,1,1-Trifluoro-4-(3-methoxyphenyl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-(3-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-4-methyl-2-(4-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-4-methyl-2-(4-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorophenyl)-4-methyl-2-(4-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-methyl-2-quinolin-4-ylmethyl-4-(3-trifluoromethylphenyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-4-methyl-2-(7-methyl-1*H*-benzoimidazol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-(3-trifluoromethylphenyl)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

5-Fluoro-2-(4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

4-(5-Bromo-4-fluoro-2-methoxyphenyl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

2-(2-Phenyl-4-methylimidazol-1-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihydrobenzofuran-7-yl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

2-(2-Phenylimidazol-1-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihydrobenzofuran-7-yl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-methyl-4-(5-methyl-2,3-dihydrobenzofuran-7-yl)-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-phenylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-(5-methyl-2,3-dihydrobenzofuran-7-yl)pentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-*m*-tolylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-naphthalen-2-ylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-*o*-tolylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-*p*-tolylpentan-2-ol;

4-(2,3-Dihydrobenzofuran-5-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(7-Bromo-2,3-dihydrobenzofuran-5-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(2,3-Dihydrobenzofuran-5-yl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(1-methoxynaphthalen-2-yl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

2-(4,4,4-Trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)naphthalen-1-ol;

1,1,1-Trifluoro-4-methyl-4-naphthalen-2-yl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-(1-methoxynaphthalen-2-yl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-methyl-2-quinolin-4-ylmethyl-4-*p*-tolylpentan-2-ol;

4-Chroman-8-yl-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-4-methyl-4-phenyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(6-Bromochroman-8-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*b*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*b*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorophenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-methyl-4-phenyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(7-fluoroquinolin-4-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-2-(7-fluoroquinolin-4-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-2-(5-fluoroquinolin-4-ylmethyl)-4-methylpentan-2-ol;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

2-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

2-[4-(5-Fluoro-2-methylphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

1,1,1-Trifluoro-4-(2-methoxyphenyl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-(2-methoxyphenyl)-4-methylpentan-2-ol;

2-[4-(5-Fluoro-2,3-dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

4-(5-Bromo-2-methoxyphenyl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(5-Bromo-2-methoxyphenyl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-(4,4,4-Trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

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1,1,1-Trifluoro-4-methyl-4-phenyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-[4-(5-Bromo-2,3-dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

4-Bromo-2-(4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-[4-(4-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethyl-pentyl]-1*H*-indole-3-carbonitrile;

2-(2-Hydroxy-4-methyl-4-phenyl-2-trifluoromethylpentyl)-4-methyl-1*H*-indole-6-carbonitrile;

2-[4-(3-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

2-[4-(4-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

2-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-methyl-4-phenyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-(2-Hydroxy-4-methyl-4-phenyl-2-trifluoromethylpentyl)-1*H*-indole-5-carbonitrile;

2-[4-(3-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

2-[4-(4-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-(5,6,7,8-tetrahydroquinolin-4-ylmethyl)pentan-2-ol;

1-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-(2-Hydroxy-4-methyl-4-phenyl-2-trifluoromethylpentyl)-1*H*-indole-3-carbonitrile;

5-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)butyl]phenol;

2-[4-(4-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(3-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

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2-[4-(4-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(5-Fluoro-2-methylphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)butyl]phenol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-methyl-4-phenylpentan-2-ol;

2-[4-(4-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carboxylic acid methyl ester;

1-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(3-methyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(3-methoxyphenyl)-4-methyl-2-(5-trifluoromethyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

2-[2-Hydroxy-4-(3-methoxyphenyl)-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)butyl]phenol;

5-Fluoro-2-[4,4,4-trifluoro-3-(7-fluoro-1*H*-indol-2-ylmethyl)-3-hydroxy-1,1-dimethylbutyl]phenol;

2-[4-(5-Fluoro-2-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(3-methyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)butyl]phenol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-thiophen-3-ylpentan-2-ol;

1,1,1-Trifluoro-4-methyl-2-quinolin-4-ylmethyl-4-thiophen-3-ylpentan-2-ol;

5-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)butyl]phenol;

1,1,1-Trifluoro-4-(3-fluorophenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

3-(4,4,4-Trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

2-[4-(5-Bromo-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carboxylic acid methyl ester;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carboxylic acid methyl ester;

4-(2,6-Dimethylphenyl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

3-[4,4,4-Trifluoro-3-hydroxy-3-(1*H*-indol-2-ylmethyl)-1,1-dimethylbutyl]phenol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihydrobenzofuran-7-yl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-[2-Hydroxy-4-(3-methoxyphenyl)-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

2-[4-(5-Bromo-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

2-[4-(4-Fluoro-2-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(5-nitro-1*H*-indol-2-ylmethyl)pentan-2-ol;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carboxylic acid amide;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carboxylic acid dimethylamide;

{2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indol-5-yl}morpholin-4-ylmethanone;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-6-carboxylic acid methyl ester; and

2-[4-(5-Fluoro-2-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-6-carboxylic acid methyl ester,

or a tautomer, prodrug, solvate, or salt thereof.

9. A compound according to claim 8, the compound selected from:

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-(2,6-Dichloropyridin-4-ylmethyl)-1,1,1-trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

4-(5-Bromo-2,3-dihydrobenzofuran-7-yl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(quinolin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ylmethyl)-4-(5-fluoro-2-methoxyphenyl)-4-methylpentan-2-ol;

4-(2,3-dihydrobenzofuran-7-yl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(4-methyl-1*H*-indol-2-ylmethyl)butyl]phenol;

4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(5-Bromo-2,3-dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

2-[3-(5,7-Dimethyl-1*H*-benzoimidazol-2-ylmethyl)-4,4,4-trifluoro-3-hydroxy-1,1-dimethylbutyl]-4-fluorophenol;

1,1,1-Trifluoro-4-(3-methoxyphenyl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-(3-methoxyphenyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-4-methyl-2-(4-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-4-methyl-2-(4-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorophenyl)-4-methyl-2-(4-methyl-1*H*-indol-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-methyl-2-quinolin-4-ylmethyl-4-(3-trifluoromethylphenyl)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-(3-trifluoromethylphenyl)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

5-Fluoro-2-(4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

4-(5-Bromo-4-fluoro-2-methoxyphenyl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihydrobenzofuran-7-yl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihydrobenzofuran-7-yl)-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-methyl-4-(5-methyl-2,3-dihydrobenzofuran-7-yl)-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-(5-methyl-2,3-dihydrobenzofuran-7-yl)pentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-*m*-tolylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methyl-4-*o*-tolylpentan-2-ol;

4-(7-Bromo-2,3-dihydrobenzofuran-5-yl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

1,1,1-Trifluoro-4-methyl-4-phenyl-2-quinolin-4-ylmethylpentan-2-ol;

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1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-2-(7-fluoroquinolin-4-ylmethyl)-4-methylpentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorophenyl)-2-(5-fluoroquinolin-4-ylmethyl)-4-methylpentan-2-ol;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

2-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

2-[4-(5-Fluoro-2-methylphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

1,1,1-Trifluoro-4-(2-methoxyphenyl)-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ylmethyl)-4-(2-methoxyphenyl)-4-methylpentan-2-ol;

2-[4-(5-Fluoro-2,3-dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

4-(5-Bromo-2-methoxyphenyl)-1,1,1-trifluoro-4-methyl-2-quinolin-4-ylmethylpentan-2-ol;

4-(5-Bromo-2-methoxyphenyl)-1,1,1-trifluoro-2-(1*H*-indol-2-ylmethyl)-4-methylpentan-2-ol;

2-(4,4,4-Trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

1,1,1-Trifluoro-4-methyl-4-phenyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-[4-(5-Bromo-2,3-dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

4-Bromo-2-(4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-quinolin-4-ylmethylbutyl)phenol;

4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-[4-(4-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethyl-pentyl]-1*H*-indole-3-carbonitrile;

2-(2-Hydroxy-4-methyl-4-phenyl-2-trifluoromethylpentyl)-4-methyl-1*H*-indole-6-carbonitrile;

2-[4-(3-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

2-[4-(4-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

2-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-methyl-4-phenyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

4-(2,3-Dihydrobenzofuran-7-yl)-1,1,1-trifluoro-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

2-(2-Hydroxy-4-methyl-4-phenyl-2-trifluoromethylpentyl)-1*H*-indole-5-carbonitrile;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-(5,6,7,8-tetrahydroquinolin-4-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-methoxyphenyl)-4-methyl-2-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)pentan-2-ol;

5-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)butyl]phenol;

2-[4-(4-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(4-Fluorophenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

2-[4-(5-Fluoro-2-methylphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[3,2-*c*]pyridin-2-ylmethyl)butyl]phenol;

1-[4-(2,3-Dihydrobenzofuran-7-yl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-3-carbonitrile;

1,1,1-Trifluoro-4-(5-fluoro-2-methylphenyl)-4-methyl-2-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(3-methyl-1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)pentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)butyl]phenol;

2-[4-(5-Fluoro-2-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

4-Fluoro-2-[4,4,4-trifluoro-3-hydroxy-1,1-dimethyl-3-(1*H*-pyrrolo[2,3-*c*]pyridin-2-ylmethyl)butyl]phenol;

2-[2-Hydroxy-4-(3-methoxyphenyl)-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

2-[4-(5-Bromo-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-4-methyl-1*H*-indole-6-carbonitrile;

2-[4-(4-Fluoro-2-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carbonitrile;

1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-2-(5-nitro-1*H*-indol-2-ylmethyl)pentan-2-ol;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carboxylic acid amide;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-5-carboxylic acid dimethylamide;

{2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indol-5-yl}morpholin-4-ylmethanone;

2-[4-(5-Fluoro-2-methoxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-6-carboxylic acid methyl ester;

2-[4-(5-Fluoro-2-hydroxyphenyl)-2-hydroxy-4-methyl-2-trifluoromethylpentyl]-1*H*-indole-6-carboxylic acid methyl ester,

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or a tautomer, prodrug, solvate, or salt thereof.

10. A pharmaceutical composition comprising an effective amount of a compound according to one of claims 1 to 10, or a tautomer, prodrug, solvate, or salt thereof, and a pharmaceutically acceptable excipient or carrier.

11. A method of modulating the glucocorticoid receptor function in a patient, the method comprising administering to the patient an effective amount of a pharmaceutically acceptable compound according to one of claims 1 to 10, or a tautomer, prodrug, solvate, or salt thereof.

12. A method of treating a disease-state or condition mediated by the glucocorticoid receptor function in a patient in need of such treatment, the method comprising administering to the patient an effective amount of a pharmaceutically acceptable compound according to one of claims 1 to 10, or a tautomer, prodrug, solvate, or salt thereof.

13. A method of treating a disease-state or condition selected from: type II diabetes, obesity, cardiovascular diseases, hypertension, arteriosclerosis, neurological diseases, adrenal and pituitary tumors, and glaucoma, in a patient in need of such treatment, the method comprising administering to the patient an effective amount of a pharmaceutically acceptable compound according to one of claims 1 to 10, or a tautomer, prodrug, solvate, or salt thereof.

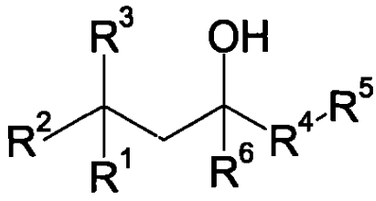
14. A method of treating a disease characterized by inflammatory, allergic, or proliferative processes, in a patient in need of such treatment, the method comprising administering to the patient an effective amount of a pharmaceutically acceptable compound according to one of claims 1 to 10, or a tautomer, prodrug, solvate, or salt thereof.

15. The method according to claim 14, wherein the disease is selected from: (i) lung diseases; (ii) rheumatic diseases/autoimmune diseases/joint diseases; (iii) allergic

diseases; (iv) vasculitis diseases; (v) dermatological diseases; (vi) renal diseases; (vii) hepatic diseases; (viii) gastrointestinal diseases; (ix) proctological diseases; (x) eye diseases; (xi) diseases of the ear, nose, and throat (ENT) area; (xii) neurological diseases; (xiii) blood diseases; (xiv) tumor diseases; (xv) endocrine diseases; (xvi) organ and tissue transplantations and graft-versus-host diseases; (xvii) severe states of shock; (xviii) substitution therapy; and (xix) pain of inflammatory genesis.

16. A method of treating a disease-state or condition mediated by the glucocorticoid receptor function in a patient in need of such treatment, the method comprising sequentially or simultaneously administering to the patient: (a) an effective amount of a pharmaceutically acceptable compound according to one of claims 1 to 10 or a tautomer, prodrug, solvate, or salt thereof; and (b) a pharmaceutically acceptable glucocorticoid.

17. A compound of Formula (IB)



(IB)

wherein:

R^1 is an aryl or heteroaryl group, each optionally independently substituted with one to three substituent groups,

wherein each substituent group of R^1 is independently C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, C_3-C_8 cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_5 alkoxy, C_2-C_5 alkenyloxy, C_2-C_5 alkynyloxy, aryloxy, acyl, C_1-C_5 alkoxycarbonyl, C_1-C_5 alkanoyloxy, C_1-C_5 alkanoyl, aroyl, aminocarbonyl, C_1-C_5 alkylaminocarbonyl, C_1-C_5 dialkylaminocarbonyl, aminocarbonyloxy, C_1-C_5 alkylaminocarbonyloxy, C_1-C_5 dialkylaminocarbonyloxy, C_1-C_5 alkanoylamino, C_1-C_5 alkoxycarbonylamino, C_1-C_5 alkylsulfonylamino, aminosulfonyl, C_1-C_5 alkylaminosulfonyl, C_1-C_5 dialkylaminosulfonyl, halogen, hydroxy, carboxy, cyano, trifluoromethyl, trifluoromethoxy, nitro, or amino wherein the nitrogen atom is optionally independently mono- or di-substituted by C_1-C_5 alkyl or aryl;

or ureido wherein either nitrogen atom is optionally independently substituted with C_1-C_5 alkyl; or C_1-C_5 alkylthio wherein the sulfur atom is optionally oxidized to a sulfoxide or sulfone,

wherein each substituent group of R^1 is optionally independently substituted with one to three substituent groups selected from methyl, methoxy, halogen, hydroxy, oxo, cyano, or amino,

R^2 and R^3 are each independently C_1-C_5 alkyl;

R^4 is C_1-C_5 alkyl, C_2-C_5 alkenyl, or C_2-C_5 alkynyl, each optionally independently substituted with one to three substituent groups,

wherein each substituent group of R^4 is independently C_1-C_3 alkyl, hydroxy, halogen, amino, or oxo;

R^5 is a heteroaryl group optionally independently substituted with one to three substituent groups,

wherein each substituent group of R^5 is independently C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, C_3-C_8 cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_5 alkoxy, C_2-C_5 alkenyloxy, C_2-C_5 alkynyloxy, aryloxy, acyl, C_1-C_5 alkoxycarbonyl, C_1-C_5 alkanoyloxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, aminocarbonyloxy, C_1-C_5 alkylaminocarbonyloxy, C_1-C_5 dialkylaminocarbonyloxy, C_1-C_5 alkanoylamino, C_1-C_5 alkoxycarbonylamino, C_1-C_5 alkylsulfonylamino, aminosulfonyl, C_1-C_5 alkylaminosulfonyl, C_1-C_5 dialkylaminosulfonyl, halogen, hydroxy, carboxy, cyano, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, nitro, or amino wherein the nitrogen atom is optionally independently mono- or di-substituted by C_1-C_5 alkyl; or ureido wherein either nitrogen atom is optionally independently substituted with C_1-C_5 alkyl; or C_1-C_5 alkylthio wherein the sulfur atom is optionally oxidized to a sulfoxide or sulfone,

wherein each substituent group of R^5 is optionally independently substituted with one to three substituent groups selected from C_1-C_3 alkyl, C_1-C_3 alkoxy, halogen, hydroxy, oxo, cyano, amino, or trifluoromethyl; and

R^6 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, carbocycle, heterocyclyl, aryl, heteroaryl, carbocycle-C_1-C_8 alkyl, aryl-C_1-C_8 alkyl, aryl-C_1-C_8 haloalkyl, heterocyclyl-C_1-C_8 alkyl, heteroaryl-C_1-C_8 alkyl, carbocycle-C_2-C_8 alkenyl, aryl-C_2-C_8 alkenyl, heterocyclyl-C_2-C_8 alkenyl, or heteroaryl-C_2-C_8 alkenyl, each optionally independently substituted with one to three substituent groups,

wherein each substituent group of R^6 is independently C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, C_3-C_8 cycloalkyl, phenyl, C_1-C_5 alkoxy, phenoxy, C_1-C_5 alkanoyl, aroyl, C_1-C_5 alkoxycarbonyl, C_1-C_5 alkanoyloxy, aminocarbonyloxy, C_1-C_5 alkylaminocarbonyloxy, C_1-C_5 dialkylaminocarbonyloxy, aminocarbonyl, C_1-C_5 alkylaminocarbonyl, C_1-C_5 dialkylaminocarbonyl, C_1-C_5 alkanoylamino, C_1-C_5 alkoxycarbonylamino, C_1-C_5 alkylsulfonylamino, C_1-C_5 alkylaminosulfonyl, C_1-C_5 dialkylaminosulfonyl, halogen, hydroxy, carboxy, cyano, oxo, trifluoromethyl, nitro, amino wherein the nitrogen atom is optionally independently mono- or di-substituted by C_1-C_5 alkyl; or ureido wherein either nitrogen atom is optionally independently substituted with C_1-C_5 alkyl; or C_1-C_5 alkylthio wherein the sulfur atom is optionally oxidized to a sulfoxide or sulfone,

wherein R^6 cannot be trifluoromethyl,

or a tautomer, prodrug, solvate, or salt thereof.

18. The compound of Formula (IB) according to claim 17, wherein:

R^1 is thienyl, phenyl, dihydrobenzofuranyl, benzofuranyl, dihydroindolyl, indolyl, dihydrobenzothienyl, benzothienyl, benzodioxolanyl, benzoxazolyl, benzisoxazolyl, benzpyrazolyl, benzimidazolyl, quinolinyl, pyridinyl, pyrimidinyl, or pyrazinyl, each optionally independently substituted with one to three substituent groups,

wherein each substituent group of R^1 is independently C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, C_1-C_3 alkoxy, C_2-C_3 alkenyloxy, C_1-C_3 alkanoyl, C_1-C_3 alkoxycarbonyl, C_1-C_3 alkanoyloxy, halogen, hydroxy, carboxy, cyano, trifluoromethyl, nitro, or C_1-C_3 alkylthio wherein the sulfur atom is optionally oxidized to a sulfoxide or sulfone,

wherein each substituent group of R^1 is optionally independently substituted with a substituent group selected from methyl, methoxy, halogen, hydroxy, oxo, cyano, or amino;

R^2 and R^3 are each independently C_1-C_3 alkyl;

R^4 is CH_2;

R^5 is a pyridyl, indolyl, azaindolyl, benzofuranyl, furanylpyridinyl, benzothienyl, thienopyridinyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, quinolinyl, or isoquinolinyl group, each optionally independently substituted with one to three substituent groups,

wherein each substituent group of R^5 is independently C_1-C_3 alkyl, C_2-C_3 alkenyl, phenyl, C_1-C_3 alkoxy, methoxycarbonyl, aminocarbonyl, C_1-C_3 alkylaminocarbonyl, C_1-C_3 dialkylaminocarbonyl, heterocyclylcarbonyl, fluoro, chloro, bromo, cyano, trifluoromethyl, or C_1-C_3 alkylthio wherein the sulfur atom is optionally oxidized to a sulfoxide or sulfone,

wherein each substituent group of R^5 is optionally independently substituted with a substituent group selected from methyl, methoxy, fluoro, chloro, bromo, cyano, or trifluoromethyl; and

R^6 is C_1-C_5 alkyl, C_2-C_5 alkenyl, C_3-C_6 cycloalkyl, phenyl, C_3-C_6 cycloalkyl-C_1-C_3 alkyl, phenyl-C_1-C_3 alkyl, phenyl-C_1-C_3 haloalkyl, C_3-C_6 cycloalkyl-C_2-C_3 alkenyl,

phenyl-C_2-C_3 alkenyl, each optionally independently substituted with one to three substituent groups,

wherein each substituent group of R^6 is independently C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, C_1-C_3 alkoxy, aminocarbonyl, C_1-C_3 alkylaminocarbonyl, C_1-C_3 dialkylaminocarbonyl, halogen, hydroxy, carboxy, cyano, trifluoromethyl, nitro, or C_1-C_3 alkylthio wherein the sulfur atom is optionally oxidized to a sulfoxide or sulfone,

or a tautomer, prodrug, solvate, or salt thereof.

19. The compound of Formula (IB) according to claim 17, wherein:

R^1 is thienyl, phenyl, pyridyl, dihydrobenzofuranyl, or benzofuranyl, each optionally independently substituted with one or two substituent groups,

wherein each substituent group of R^1 is independently methyl, ethyl, methoxy, ethoxy, fluoro, chloro, bromo, hydroxy, trifluoromethyl, or cyano;

R^2 and R^3 are each methyl;

R^4 is CH_2;

R^5 is a pyridyl, indolyl, azaindolyl, benzofuranyl, benzoxazolyl, benzimidazolyl, quinolinyl, or isoquinolinyl group, each optionally independently substituted with one to three substituent groups,

wherein each substituent group of R^5 is independently methyl, phenyl ,methoxycarbonyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, morpholinylcarbonyl, fluoro, chloro, cyano, or trifluoromethyl; and

R^6 is C_1-C_5 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl-methyl-, or benzyl, each optionally independently substituted with one to three substituent groups,

wherein each substituent group of R^6 is independently methyl, methoxy, fluoro, chloro, bromo, cyano, trifluoromethyl, or hydroxy,

or a tautomer, prodrug, solvate, or salt thereof.

20. The compound of Formula (IB) according to claim 17, wherein:

R^1 is thienyl, phenyl, dihydrobenzofuranyl, or benzofuranyl, each optionally independently substituted with one to three substituent groups,

wherein each substituent group of R^1 is independently C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, C_1-C_3 alkoxy, C_2-C_3 alkenyloxy, C_1-C_3 alkanoyl, C_1-C_3 alkoxycarbonyl, C_1-C_3 alkanoyloxy, halogen, hydroxy, carboxy, cyano, trifluoromethyl, nitro, or C_1-C_3 alkylthio wherein the sulfur atom is optionally oxidized to a sulfoxide or sulfone; and

R^2 and R^3 are each independently C_1-C_3 alkyl,

or a tautomer, prodrug, solvate, or salt thereof.

21. A compound selected from:

2-Cyclopropyl-4-(5-fluoro-2-methoxyphenyl)-1-(1*H*-indol-2-yl)-4-methylpentan-2-ol;

5-(5-Fluoro-2-methoxyphenyl)-3-(1*H*-indol-2-ylmethyl)-2,5-dimethylhexan-3-ol;

5-(5-Fluoro-2-methoxyphenyl)-3-(1*H*-indol-2-ylmethyl)-5-methylhexan-3-ol;

2-Cyclohexylmethyl-1-(4,6-dimethyl-pyridin-2-yl)-4-(5-fluoro-2-methoxy-phenyl)-4-methyl-pentan-2-ol;

2-Cyclohexylmethyl-4-(5-fluoro-2-methoxy-phenyl)-1-(1*H*-indol-2-yl)-4-methyl-pentan-2-ol;

7-(5-Fluoro-2-methoxyphenyl)-5-(indol-2-ylmethyl)-7-methyloctan-5-ol;

2-(Benzimidazol-2-ylmethyl)-4-methyl-4-(pyrrol-1-yl)pentan-2-ol;

1-(1*H*-Benzoimidazol-2-yl)-2-cyclohexylmethyl-4-(5-fluoro-2-methoxy-phenyl)-4-methyl-pentan-2-ol;

5-(5-Fluoro-2-methoxyphenyl)-3-(benzimidazol-2-ylmethyl)-2,2,5-trimethylhexan-3-ol;

4-(5-Fluoro-2-methoxyphenyl)-2-fluoromethyl-1-(1*H*-indol-2-yl)-4-methylpentan-2-ol;

2-Cyclopropyl-4-(2,3-dihydrobenzofuran-7-yl)-1-(1*H*-indol-2-yl)-4-methylpentan-2-ol;

2-Cyclopropyl-4-(2,3-dihydrobenzofuran-7-yl)-1-(quinolin-4-yl)-4-methylpentan-2-ol;

2-Cyclopropyl-4-(5-fluoro-2-methoxyphenyl)-1-(6-cyano-4-methylindol-2-yl)-4-methylpentan-2-ol;

2-Cyclopropyl-4-(5-fluoro-2-methoxyphenyl)-4-methyl-1-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)pentan-2-ol;

4-(5-Bromo-2,3-dihydrobenzofuran-7-yl)-2-cyclopropyl-4-methyl-1-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)pentan-2-ol,

or a tautomer, prodrug, solvate, or salt thereof.

22. A compound according to claim 21, the compound selected from:

2-Cyclopropyl-4-(5-fluoro-2-methoxyphenyl)-1-(1*H*-indol-2-yl)-4-methylpentan-2-ol;

5-(5-Fluoro-2-methoxyphenyl)-3-(indol-2-ylmethyl)-2,5-dimethylhexan-3-ol;

5-(5-Fluoro-2-methoxyphenyl)-3-(indol-2-ylmethyl)-5-methylhexan-3-ol;

2-Cyclohexylmethyl-4-(5-fluoro-2-methoxyphenyl)-1-(1*H*-indol-2-yl)-4-methylpentan-2-ol;

5-(5-Fluoro-2-methoxyphenyl)-3-(benzimidazol-2-ylmethyl)-2,2,5-trimethylhexan-3-ol;

4-(5-Fluoro-2-methoxyphenyl)-2-fluoromethyl-1-(1*H*-indol-2-yl)-4-methylpentan-2-ol;

2-Cyclopropyl-4-(2,3-dihydrobenzofuran-7-yl)-1-(1*H*-indol-2-yl)-4-methylpentan-2-ol;

2-Cyclopropyl-4-(2,3-dihydrobenzofuran-7-yl)-1-(quinolin-4-yl)-4-methylpentan-2-ol;

2-Cyclopropyl-4-(5-fluoro-2-methoxyphenyl)-1-(6-cyano-4-methylindol-2-yl)-4-methylpentan-2-ol;

2-Cyclopropyl-4-(5-fluoro-2-methoxyphenyl)-4-methyl-1-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)pentan-2-ol; and

4-(5-Bromo-2,3-dihydrobenzofuran-7-yl)-2-cyclopropyl-4-methyl-1-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)pentan-2-ol,

or a tautomer, prodrug, solvate, or salt thereof.

23. A compound according to claim 22, the compound selected from:

5-(5-Fluoro-2-methoxyphenyl)-3-(benzimidazol-2-ylmethyl)-2,2,5-trimethylhexan-3-ol;

4-(5-Fluoro-2-methoxyphenyl)-2-fluoromethyl-1-(1*H*-indol-2-yl)-4-methylpentan-2-ol;

2-Cyclopropyl-4-(5-fluoro-2-methoxyphenyl)-1-(1*H*-indol-2-yl)-4-methylpentan-2-ol;

5-(5-Fluoro-2-methoxyphenyl)-3-(indol-2-ylmethyl)-2,5-dimethylhexan-3-ol;

5-(5-Fluoro-2-methoxyphenyl)-3-(indol-2-ylmethyl)-5-methylhexan-3-ol; and

2-Cyclopropyl-4-(5-fluoro-2-methoxyphenyl)-4-methyl-1-(1*H*-pyrrolo[2,3-*c*]pyridin-2-yl)pentan-2-ol,

or a tautomer, prodrug, solvate, or salt thereof.

24. A pharmaceutical composition comprising an effective amount of a compound according to one of claims 17 to 23, or a tautomer, prodrug, solvate, or salt thereof, and a pharmaceutically acceptable excipient or carrier.

25. A method of modulating the glucocorticoid receptor function in a patient, the method comprising administering to the patient an effective amount of a pharmaceutically acceptable compound according to one of claims 17 to 23, or a tautomer, prodrug, solvate, or salt thereof.

26. A method of treating a disease-state or condition mediated by the glucocorticoid receptor function in a patient in need of such treatment, the method comprising administering to the patient an effective amount of a pharmaceutically acceptable compound according to one of claims 17 to 23, or a tautomer, prodrug, solvate, or salt thereof.

27. A method of treating a disease-state or condition selected from: type II diabetes, obesity, cardiovascular diseases, hypertension, arteriosclerosis, neurological diseases, adrenal and pituitary tumors, and glaucoma, in a patient in need of such treatment, the method comprising administering to the patient an effective amount of a pharmaceutically acceptable compound according to one of claims 17 to 23, or a tautomer, prodrug, solvate, or salt thereof.

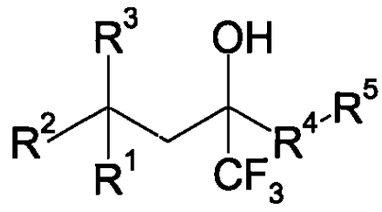
28. A method of treating a disease characterized by inflammatory, allergic, or proliferative processes, in a patient in need of such treatment, the method comprising administering to the patient an effective amount of a pharmaceutically acceptable compound according to one of claims 17 to 23, or a tautomer, prodrug, solvate, or salt thereof.

29. The method according to claim 28, wherein the disease is selected from: (i) lung diseases; (ii) rheumatic diseases/autoimmune diseases/joint diseases; (iii) allergic diseases; (iv) vasculitis diseases; (v) dermatological diseases; (vi) renal diseases; (vii) hepatic diseases; (viii) gastrointestinal diseases; (ix) proctological diseases; (x) eye diseases; (xi) diseases of the ear, nose, and throat (ENT) area; (xii) neurological diseases; (xiii) blood diseases; (xiv) tumor diseases; (xv) endocrine diseases; (xvi) organ and tissue transplantations and graft-versus-host diseases; (xvii) severe states of shock; (xviii) substitution therapy; and (xix) pain of inflammatory genesis.

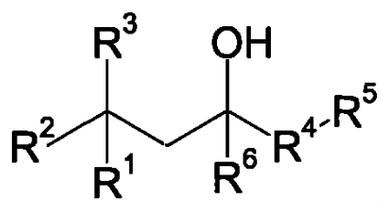
30. A method of treating a disease-state or condition mediated by the glucocorticoid receptor function in a patient in need of such treatment, the method comprising sequentially or simultaneously administering to the patient: (a) an effective amount of a pharmaceutically acceptable compound according to one of claims 17 to 23 or a tautomer, prodrug, solvate, or salt thereof; and (b) a pharmaceutically acceptable glucocorticoid.

Abstract

Compounds of Formula (IA) and Formula (IB)



(IA)



(IB)

wherein R^1, R^2, R^3, R^4, R^5, and R^6 are as defined herein for Formula (IA) or Formula (IB), or a tautomer, prodrug, solvate, or salt thereof; pharmaceutical compositions containing such compounds, and methods of modulating the glucocorticoid receptor function and methods of treating disease-states or conditions mediated by the glucocorticoid receptor function or characterized by inflammatory, allergic, or proliferative processes in a patient using these compounds.

PCT REQUEST 9/240PCT

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0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	

0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.01.2003)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	United States Patent and Trademark Office (USPTO) (RO/US)
0-7	Applicant's or agent's file reference	9/240PCT
I	Title of invention	GLUCOCORTICOID MIMETICS, METHODS OF MAKING THEM, PHARMACEUTICAL COMPOSITIONS, AND USES THEREOF
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States
II-4	Name	BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.
II-5	Address:	900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877-0368 United States of America
II-6	State of nationality	US
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II-8	Telephone No.	203-798-4868
II-9	Facsimile No.	203-798-4408
III-1	Applicant and/or inventor	
III-1-1	This person is:	inventor only
III-1-4	Name (LAST, First)	BEKKALI, Younes
III-1-5	Address:	Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877-0368 United States of America

III-2	Applicant and/or inventor	
III-2-1	This person is:	inventor only
III-2-4	Name (LAST, First)	BETAGERI, Raj
III-2-5	Address:	Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877-0368 United States of America
III-3	Applicant and/or inventor	
III-3-1	This person is:	inventor only
III-3-4	Name (LAST, First)	GILMORE, Thomas, A.
III-3-5	Address:	12 Andover Street Salem, MA 01970 United States of America
III-4	Applicant and/or inventor	
III-4-1	This person is:	inventor only
III-4-4	Name (LAST, First)	CARDOZO, Mario, G.
III-4-5	Address:	579 Miramar Avenue San Francisco, CA 94112 United States of America
III-5	Applicant and/or inventor	
III-5-1	This person is:	inventor only
III-5-4	Name (LAST, First)	KIRRANE, Thomas, M.
III-5-5	Address:	Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877-0368 United States of America
III-6	Applicant and/or inventor	
III-6-1	This person is:	inventor only
III-6-4	Name (LAST, First)	KUZMICH, Daniel
III-6-5	Address:	Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877-0368 United States of America

III-7	Applicant and/or inventor	
III-7-1	This person is:	inventor only
III-7-4	Name (LAST, First)	PROUDFOOT, John, Robert
III-7-5	Address:	Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877-0368 United States of America
III-8	Applicant and/or inventor	
III-8-1	This person is:	inventor only
III-8-4	Name (LAST, First)	TAKAHASHI, Hidenori
III-8-5	Address:	Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877-0368 United States of America
III-9	Applicant and/or inventor	
III-9-1	This person is:	inventor only
III-9-4	Name (LAST, First)	THOMSON, David
III-9-5	Address:	Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877-0368 United States of America
III-10	Applicant and/or inventor	
III-10-1	This person is:	inventor only
III-10-4	Name (LAST, First)	WANG, Ji
III-10-5	Address:	Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877-0368 United States of America
III-11	Applicant and/or inventor	
III-11-1	This person is:	inventor only
III-11-4	Name (LAST, First)	ZINDELL, Renee
III-11-5	Address:	Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877-0368 United States of America

III-12	Applicant and/or inventor	
III-12-1	This person is:	inventor only
III-12-4	Name (LAST, First)	HARCKEN, Christian, Hanke, Justus, Joachim
III-12-5	Address:	Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877-0368 United States of America
III-13	Applicant and/or inventor	
III-13-1	This person is:	inventor only
III-13-4	Name (LAST, First)	RIETHER, Doris
III-13-5	Address:	Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877-0368 United States of America
IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	RAYMOND, Robert, P.
IV-1-2	Address:	Boehringer Ingelheim Corporation 900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877-0368 United States of America
IV-1-3	Telephone No.	203-798-9988
IV-1-4	Facsimile No.	203-798-4408
IV-1-5	Agent's registration No.	25,089
IV-2	Additional agent(s)	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	DEVLIN, Mary-Ellen, M.(27,928); STEMPEL, Alan, R.(28,991); BOTTINO, Anthony, P.(41,629); POCCHIARI, Susan, K.(45,016); DATLOW, Philip, I.(41,482); WITKOWSKI, Timothy, X.(40,232); DOW, David, A.(46,124)

V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT SE SI SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW
V-5	Precautionary Designation Statement In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-6	Exclusion(s) from precautionary designations	NONE
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	26 March 2002 (26.03.2002)
VI-1-2	Number	60/367,758
VI-1-3	Country	US

VI-2	Priority claim of earlier national application		
VI-2-1	Filing date	09 December 2002 (09.12.2002)	
VI-2-2	Number	60/431,817	
VI-2-3	Country	US	
VI-3	Priority claim of earlier national application		
VI-3-1	Filing date	24 January 2003 (24.01.2003)	
VI-3-2	Number	60/442,404	
VI-3-3	Country	US	
VI-4	Priority document request		
	The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1, VI-2, VI-3	
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)	
VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	7	-
IX-2	Description	186	-
IX-3	Claims	84	-
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	0	-
IX-7	TOTAL	278	
	Accompanying Items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-11	Copy of general power of attorney	✓	-
IX-17	PCT-EASY diskette	-	Diskette
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	

PCT REQUEST 9/240PCT

Original (for SUBMISSION) - printed on 21.03.2003 11:49:10 AM

X-1	Signature of applicant, agent or common representative	Timothy Witkowski
X-1-1	Name (LAST, First)	WITKOWSKI, Timothy, X.

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	

PCT (ANNEX - FEE CALCULATION SHEET) 9/240PCT

Original (for SUBMISSION) - printed on 21.03.2003 11:49:10 AM

(This sheet is not part of and does not count as a sheet of the international application)

0	For receiving Office use only	
0-1	International Application No.	
0-2	Date stamp of the receiving Office	

0-4	Form - PCT/RO/101 (Annex) PCT Fee Calculation Sheet				
0-4-1	Prepared using		PCT-EASY Version 2.92 (updated 01.01.2003)		
0-9	Applicant's or agent's file reference		9/240PCT		
2	Applicant		BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.		
12	Calculation of prescribed fees		fee amount/multiplier	Total amounts (USD)	
12-1	Transmittal fee	T	⇨	240	
12-2-1	Search fee	S	⇨	936	
12-2-2	International search to be carried out by		EP		
12-3	International fee				
	Basic fee				
	(first 30 sheets)	b1	407		
12-4	Remaining sheets		248		
12-5	Additional amount	(X)	9		
12-6	Total additional amount	b2	2,232		
12-7	b1 + b2 =	B	2,639		
12-8	Designation fees				
	Number of designations contained in international application		94		
12-9	Number of designation fees payable (maximum 5)		5		
12-10	Amount of designation fee	(X)	88		
12-11	Total designation fees	D	440		
12-12	PCT-EASY fee reduction	R	-125		
12-13	Total international fee (B+D-R)	I	⇨	2,954	
12-14	Fee for priority document				
	Number of priority documents requested		3		
12-15	Fee per document	(X)	20		
12-16	Total priority document fee	P	⇨	60	
12-17	TOTAL FEES PAYABLE (T+S+I+P)		⇨	4,190	
12-19	Mode of payment		authorization to charge deposit account		
12-20	Deposit account instructions				
	The receiving Office:		United States Patent and Trademark Office (USPTO) (RO/US)		
12-20-1	Authorization to charge the total fees indicated above.		✓		

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PCT (ANNEX - FEE CALCULATION SHEET) 9/240PCT

Original (for SUBMISSION) - printed on 21.03.2003 11:49:10 AM

12-20-2	Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	✓
12-20-3	Authorization to charge the fee for priority document.	✓
12-21	Deposit account No.	02-2955
12-22	Date	21 March 2003 (21.03.2003)
12-23	Name and signature	WITKOWSKI, Timothy, X. Timothy Witkowski

VALIDATION LOG AND REMARKS

13-2-2	Validation messages States	Green? More designations could be made. The following States have not been designated: US. Please verify.
13-2-7	Validation messages Contents	Green? The international application contains no drawings. Please verify.
		Green? Reference number for attached copy of general power of attorney not indicated.
13-2-9	Validation messages Payment	Green? Please ensure that you have a valid deposit account with the receiving Office selected.

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PATENT COOPERATION TREATY

RECEIVED
JUL - 1 2003
PCT PATENT SECTION

From the INTERNATIONAL SEARCHING AUTHORITY

To:
BOEHRINGER INGELHEIM CORPORATION
Attn. Raymond, Robert P.
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877-0368
UNITED STATES OF AMERICA

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION TXW

(PCT Rule 44.1)

FILE DEMAND - LD = 10/26/2003
ENTERS NAT'L PH - 9/26/2004

Applicant's or agent's file reference 9/240PCT	Date of mailing *(day/month/year)* 26/06/2003
International application No. PCT/US 03/08901	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
Applicant BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.	International filing date *(day/month/year)* 21/03/2003

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

   Where? Directly to the International Bureau of WIPO
   34, chemin des Colombettes
   1211 Geneva 20, Switzerland
   Fascimile No.: (41-22) 740.14.35

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

   Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

   Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Panayota Georgakopoulou

Form PCT/ISA/220 (July 1998)

received

NOTES TO FORM PCT/ISA/220

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These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
9/240PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 03/ 08901	21/03/2003	26/03/2002
Applicant		
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/08901

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/44 A61K31/426 A61K31/421 A61P29/00 A61P37/06
C07D213/30 C07D277/24 C07D263/32 C07D277/64 C07D263/56
C07D307/80 C07D333/16 C07D239/26 C07D215/14 C07D231/12

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 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	US 6 323 199 B1 (KALKBRENNER FRANK ET AL) 27 November 2001 (2001-11-27) cited in the application claims	1-30

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 June 2003	26/06/2003

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	Johnson, C

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/08901

299

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D233/54 C07D261/18 C07D241/12 C07D209/12 C07D237/08
C07D213/61 C07D213/84 C07D217/16 C07D413/06 C07D401/06

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)

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 June 2003	

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	Johnson, C

1

Form PCT/ISA/210 (second sheet) (July 1992)

Continuation of Box I.2

Claims Nos.: 1-14, 16-28, 30 (all part)

Present claims 1-14,16-28,30 relate to a compound defined by reference to a desirable characteristic or property, namely prodrugs. The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds of formulae (IA) and (IB) and their ester and amide analogues (see p. 102, l. 16).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/08901

30

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

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

Although claims 11-16,25-30 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-14, 16-28, 30 (all part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

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

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

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

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

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

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

Remark on Protest

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

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 03/08901

302

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6323199 B1	27-11-2001	DE 19856475 A1	31-05-2000
		AU 1976000 A	19-06-2000
		BG 105527 A	28-02-2002
		BR 9915755 A	28-08-2001
		CA 2352367 A1	08-06-2000
		CN 1334809 T	06-02-2002
		CZ 20011866 A3	12-09-2001
		EE 200100283 A	15-08-2002
		WO 0032584 A2	08-06-2000
		EP 1133486 A2	19-09-2001
		HU 0104578 A2	29-04-2002
		JP 2002531446 T	24-09-2002
		NO 20012562 A	26-07-2001
		PL 348329 A1	20-05-2002

PATENT COOPERATION TREATY

303

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF RECEIPT OF RECORD COPY

(PCT Rule 24.2(a))

To:

RAYMOND, Robert, P.
Boehringer Ingelheim Corporation
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368
United States of America

TVW

FILE DEMAND - LD = 10/26/2003
ENTER N.P. - 9/26/2003

Date of mailing (day/month/year)	IMPORTANT NOTIFICATION
12 May 2003 (12.05.03)	
Applicant's or agent's file reference	**International application No.**
9/240PCT	PCT/US03/08901

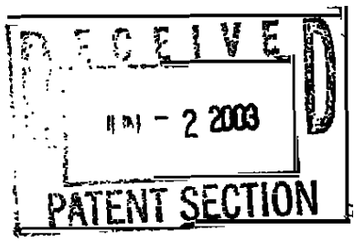
The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.(all designated States)

International filing date	:	21 March 2003 (21.03.03)
Priority date(s) claimed	:	26 March 2002 (26.03.02) 09 December 2002 (09.12.02) 24 January 2003 (24.01.03)
Date of receipt of the record copy by the International Bureau	:	25 April 2003 (25.04.03)
List of designated Offices	:	

AP :GH,GM,KE,LS,MW,MZ,SD,SL,SZ,TZ,UG,ZM,ZW
EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
EP :AT,BE,BG,CH,CY,CZ,DE,DK,EE,ES,FI,FR,GB,GR,HU,IE,IT,LU,MC,NL,PT,RO,SE,SI,SK,TR
OA :BF,BJ,CF,CG,CI,CM,GA,GN,GQ,GW,ML,MR,NE,SN,TD,TG
National :AE,AG,AL,AM,AT,AU,AZ,BA,BB,BG,BR,BY,BZ,CA,CH,CN,CO,CR,CU,CZ,DE,DK,DM,DZ, EC,EE,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KP,KR,KZ,LC,LK,LR,LS,LT,LU, LV,MA,MD,MG,MK,MN,MW,MX,MZ,NI,NO,NZ,OM,PH,PL,PT,RO,RU,SC,SD,SE,SG,SK,SL,TJ,TM,TN, TR,TT,TZ,UA,UG,UZ,VC,VN,YU,ZA,ZM,ZW



The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 338.87.20

Authorized officer:

El Mostafa MOUSSAID (Fax 338-87-20)

Telephone No. (41-22) 338 9242

received

005634571

304

Continuation of Form PCT/IB/301

NOTIFICATION OF RECEIPT OF RECORD COPY

Date of mailing (day/month/year)	IMPORTANT NOTIFICATION
12 May 2003 (12.05.03)	
Applicant's or agent's file reference	**International application No.**
9/240PCT	PCT/US03/08901

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- [X] time limits for entry into the national phase - **see updated important information (as of April 2002)**
- [X] confirmation of precautionary designations (if applicable)
- [ ] requirements regarding priority documents (if applicable)

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

PATENT COOPERATION TREATY

305

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

RAYMOND, Robert, P.
Boehringer Ingelheim Corporation
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368
United States of America

Date of mailing (day/month/year) 12 May 2003 (12.05.03)	
Applicant's or agent's file reference 9/240PCT	**IMPORTANT NOTIFICATION**
International application No. PCT/US03/08901	International filing date (day/month/year) 21 March 2003 (21.03.03)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 26 March 2002 (26.03.02)

Applicant

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
26 Marc 2002 (26.03.02)	60/367,758	US	24 Apri 2003 (24.04.03)
09 Dece 2002 (09.12.02)	60/431,817	US	24 Apri 2003 (24.04.03)
24 Janu 2003 (24.01.03)	60/442,404	US	24 Apri 2003 (24.04.03)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 338.87.20

Authorized officer

El Mostafa MOUSSAID (Fax 338-87-20)

Telephone No. (41-22) 338 9242

ANNEX TO FORM PCT/IB/301

International application No.
PCT/US03/08901

INFORMATION ON TIME LIMITS FOR ENTERING THE NATIONAL PHASE

The applicant is reminded that the "national phase" must be entered before each of the designated Offices indicated on the cover sheet of this Notification by paying national fees and furnishing translations, as prescribed by Articles 22 and 39 and the applicable national laws. In addition, the applicant may also have to comply with other special requirements applicable in certain Offices. It is the applicant's responsibility to ensure the necessary steps to enter the national phase are taken in a timely fashion. Most Offices do not issue reminders to applicants in connection with the entry into the national phase.

The applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 30 MONTHS from the priority date, not only in respect of any elected Office where a demand for international preliminary examination is filed before the expiration of 19 months from the priority date (see Article 39(1)), but also in respect of any designated Office, in the absence of filing of such demand, where Article22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see PCT Gazette No. 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the PCT Newsletter, October and November 2001 and February 2002 issues.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the PCT Gazette("Section IV" part published on a weekly basis), to the PCT Newsletter (on a monthly basis) and to the relevant National Chapters in Volume II of the PCT Applicant's Guide (the paper version of which is updated usually twice a year and the Internet version of which is updated usually on a weekly basis). Finally, a cumulative table of all applicable time limits for entering the national phase is available from WIPO's Internet site, via links from various pages the site including those of the Gazette, Newsletter and Guide, at http://www.wipo.int/pct/en/index.html.

Information about the requirements for filing a demand for international preliminary examination is set out in the PCT Applicant's Guide, Volume I/A, Chapter IX. Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

CONFIRMATION OF PRECAUTIONARY DESIGNATIONS

This notification lists only specific designations made under Rule 4.9(a) in the request. It is important to check that these designations are correct. Errors in designations can be corrected where precautionary designations have been made under Rule 4.9(b). The applicant is hereby reminded that any precautionary designations may be confirmed according to Rule 4.9(c) before the expiration of 15 months from the priority date (this time limit may not be extended). If it is not confirmed, it will automatically be regarded as withdrawn by the applicant. There will be no reminder and no invitation. Confirmation of a designation consists of the filing of a notice specifying the designated State concerned (with indication of the kind of protection or treatment desired) and the payment of the designation and confirmation fees. The Notice of confirmation and payment must reach the receiving Office within the 15-month time limit.

REQUIREMENTS REGARDING PRIORITY DOCUMENTS

For applicants who have not yet complied with the requirements regarding priority documents, the following is recalled.

Where the priority of an earlier national, regional or international application is claimed, the applicant must submit a copy of the said earlier application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 16 months from the priority date, provided that any such priority document may still be submitted to the International Bureau before that date of international publication of the international application, in which case that document will be considered to have been received by the International Bureau on the last day of the 16-month time limit (Rule 17.1(a)).

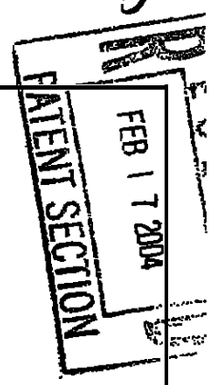
Where the priority document is issued by the receiving Office, the applicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such request must be made before the expiration of the 16-month time limit and may be subjected by the receiving Office to the payment of a fee (Rule 17.1(b)).

If the priority document concerned is not submitted to the International Bureau or if the request to the receiving Office to prepare and transmit the priority document has not been made (and the corresponding fee, if any, paid) within the applicable time limit indicated under the preceding paragraphs, any designated State may disregard the priority claim, provided that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within the time limit which is reasonable under the circumstances.

Where several priorities are claimed, the priority date to be considered for the purposes of computing the 16-month time limit is the filing date of the earliest application whose priority is claimed.

PATENT COOPERATION TREATY

TXW 307



PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

RAYMOND, Robert, P.
Boehringer Ingelheim Corporation
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368
United States of America

ENTRD DATL PHASE - 9/26/2004

Date of mailing (day/month/year) 03 February 2004 (03.02.2004)	
Applicant's or agent's file reference 9/240PCT	**IMPORTANT NOTIFICATION**
International application No. PCT/US2003/008901	**International filing date** (day/month/year) 21 March 2003 (21.03.2003)

1. The following indications appeared on record concerning:

☐ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address	State of Nationality	State of Residence
RAZAVI, Hossein Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877-0368 United States of America	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:
The above-mentioned new inventor should be added to the records.

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☒ the International Preliminary Examining Authority
☐ the designated Offices concerned
☒ the elected Offices concerned
☐ other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Beatriz LARGO (Fax 338-87-20)
Facsimile No. (41-22) 338.87.20	Telephone No. (41-22) 338 9572

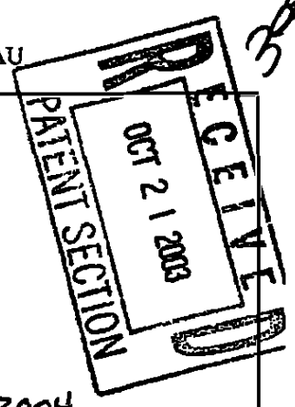
Form PCT/IB/306 (March 1994)

received 2/19/04

006082437

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU



PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

RAYMOND, Robert, P.
Boehringer Ingelheim Corporation
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368
ETATS-UNIS D'AMERIQUE

ELIMS DAT'L PH- 9/26/2004

Date of mailing *(day/month/year)*	
09 October 2003 (09.10.03)	
Applicant's or agent's file reference	IMPORTANT NOTICE
9/240PCT	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US03/08901	21 March 2003 (21.03.03)	26 March 2002 (26.03.02)

Applicant

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:

   AU, AZ, BY, CH, CN, CO, DE, DZ, HU, JP, KG, KP, KR, MD, MK, MZ, RU, TM

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

   AE, AG, AL, AM, AP, AT, BA, BB, BG, BR, BZ, CA, CR, CU, CZ, DK, DM, EA, EC, EE, EP, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, KE, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MG, MN, MW, MX, NI, NO, NZ, OA, OM, PH, PL, PT, RO, SC, SD, SE, SG, SK, SL, TJ, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW

   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-*bis*)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on 09 October 2003 (09.10.03) under No. 03/082280

4. **TIME LIMITS for filing a demand for international preliminary examination and for entry into the national phase**

   The applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be **30 MONTHS** from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of **19 months** from the priority date, but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see *PCT Gazette* No. 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the *PCT Newsletter*, October and November 2001 and February 2002 issues.

   In practice, **time limits other than the 30-month time limit** will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For **regular updates on the applicable time limits** (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at http://www.wipo.int/pct/en/index.html.

   For filing **a demand for international preliminary examination**, see the *PCT Applicant's Guide*, Volume I/A, Chapter IX. Only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

   It is the applicant's **sole responsibility** to monitor all these time limits.

received
10/27/03 kc

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Judith Zahra
Facsimile No.(41-22) 740.14.35	Telephone No.(41-22) 338.91.11

RECEIVED
NOV 14 2003
PATENT SECTION PCT

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

To:

RAYMOND, Robert, P.
Boehringer Ingelheim Corporation
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368
United States of America

EJTRS DUE - 9/26/2004

INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

Date of mailing (day/month/year)	
31 October 2003 (31.10.03)	

Applicant's or agent's file reference	IMPORTANT INFORMATION
9/240PCT	

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US03/08901	21 March 2003 (21.03.03)	26 March 2002 (26.03.02)

Applicant
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

   EP :AT,BE,BG,CH,CY,CZ,DE,DK,EE,ES,FI,FR,GB,GR,HU,IE,IT,LU,MC,NL,PT,RO,SE,
   SI,SK,TR
   National :BG,CA,CN,DE,GB,IL,JP,KP,KR,MN,NO,PL,RO,RU,SK

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

   AP :GH,GM,KE,LS,MW,MZ,SD,SL,SZ,TZ,UG,ZM,ZW
   EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
   OA :BF,BJ,CF,CG,CI,CM,GA,GN,GQ,GW,ML,MR,NE,SN,TD,TG
   National :AE,AG,AL,AM,AT,AU,AZ,BA,BB,BR,BY,BZ,CH,CO,CR,CU,CZ,DK,DM,DZ,EC,
   EE,ES,FI,GD,GE,GH,GM,HR,HU,ID,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,
   MG,MK,MW,MX,MZ,NI,NZ,OM,PH,PT,SC,SD,SE,SG,SL,TJ,TM,TN,TR,TT,TZ,UA,UG,UZ,
   VC,VN,YU,ZA,ZM,ZW

3. The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing , if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

   Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

   The entry into the European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent.

received
11/21/03

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 338.87.20

Authorized officer:
Pascal Piriou (Fax 338-87-20)

Telephone No. (41-22) 338 8188

3/0

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ EPO

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference: 9/240PCT

International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/US03/08901	21 March 2003	26 March 2002

Title of invention: Glucocorticoid Mimetics, Methods of Making them, Pharmaceutical Compositions, And Uses Thereof

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.
900 Ridgebury Road, P.O. Box 368
Ridgefield, Connecticut USA 06877-0368

Telephone No.: 203-798-9988
Facsimile No.: 203-798-4408
Teleprinter No.:
Applicant's registration No. with the Office:

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
	US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

☐ Further applicants are indicated on a continuation sheet.

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☑ agent ☐ common representative

and ☑ has been appointed earlier and represents the applicant(s) also for international preliminary examination.

☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

RAYMOND, Robert P.; STEMPEL, Alan R.; DEVLIN, Mary-Ellen M.; BOTTINO, Anthony P.; POCCHIARI, Susan K.; DATLOW, Philip I.; WITKOWSKI, Timothy X.; DOW, David A.; MORRIS, Michael
c/o BOEHRINGER INGELHEIM CORPORATION
900 Ridgebury Road, P.O. Box 368
Ridgefield, Connecticut 06877-0368 USA

Telephone No.
203-798-9988

Facsimile No.
203/798-4408

Teleprinter No.

Agent's registration No. with the Office

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

☑ the international application as originally filed

the description
☑ as originally filed
☐ as amended under Article 34

the claims
☑ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34

the drawings
☐ as originally filed
☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

☑ which is the language in which the international application was filed.

☐ which is the language of a translation furnished for the purposes of international search.

☐ which is the language of publication of the international application.

☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes not to elect:

Sheet No. 3

International application No.
PCT/US03/08901

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:			For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:	sheets	☐	☐
2. amendments under Article 34	:	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:	sheets	☐	☐
5. letter	:	sheets	☐	☐
6. other *(specify)* *Request For Detailed Exam*	:	1 sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☑ fee calculation sheet
2. ☐ original separate power of attorney
3. ☐ original general power of attorney
4. ☐ copy of general power of attorney; reference number, if any:
5. ☐ statement explaining lack of signature
6. ☐ sequence listing in computer readable form
7. ☐ other *(specify)*:

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

Timothy Witkowski

Timothy X. Witkowski, Agent

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:
2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):
3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

PATENT COOPERATION TREATY

TXW 313

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Raymond, Robert P.
BOEHRINGER INGELHEIM CORPORATION
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877-0368
ETATS-UNIS D'AMERIQUE

SUBS DAT'L PH - 9/26/2004

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	18.11.2003
Applicant's or agent's file reference 9/240PCT	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US03/08901	21.03.2003	26.03.2002

Applicant
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

   The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

   Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

   For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

   The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Ambroa, J.R.

Tel. +49 89 2399-8012

RECEIVED
NOV 21 2003
NOTICE OF ACCEPTANCE

Form PCT/IPEA/416 (July 1992)

received
11/24/03

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
9/240PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US03/08901	21.03.2003	26.03.2002
International Patent Classification (IPC) or both national classification and IPC		
A61K31/44		
Applicant		
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18.09.2003	18.11.2003
Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Johnson, C Telephone No. +49 89 2399-8287

Form PCT/IPEA/409 (Cover Sheet) (January 1994)

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US03/08901

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-186 as originally filed

Claims, Numbers

1-30 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT International application No. PCT/US03/08901

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-30 (part)

   because:

   ☒ the said international application, or the said claims Nos. 11-16,25-30 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-14,16-28,30 (all part) are so unclear that no meaningful opinion could be formed *(specify)*:

   see separate sheet

   ☒ the claims, or said claims Nos. 1-14,16-28,30 (all part) are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-30
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-30
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-10,17-24
	No:	Claims	

2. Citations and explanations

see separate sheet

III. Non-establishment of opinion

The claims are not considered to fulfil the requirements of Articles 5 and 6 PCT because of the use of the term "prodrug" (see International Search Report for details). Claims 1-14, 16-28 and 30 have therefore not been searched completely. The following examination has been performed for searched subject matter only. Claims 11-16, 25-30 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

V. Reasoned statement

Reference is made to the following document:
D1: US-B-6 323 199

Novelty

The subject matter of claims 1 and 17 differs from that of D1 because there is no amino group separating the R^5 heteroaryl group from the R^4 group. Claims 1-30 therefore fulfil the requirements of Article 33(2) PCT.

Inventive step

D1 discloses compounds with affinity for the glucocorticoid receptor for use as antiinflammatory agents. The technical problem to be solved by the present invention appears to be the provision of further compounds with this activity. In the absence of any disclosure showing that the amino group of D1 is not essential for the biological activity, those of the presently claimed compounds which have the desired activity may be considered inventive. It should be noted that all the exemplified compounds appear to have R^4 = methylene. It may be necessary in the regional phase of examination to provide evidence showing that compounds of claims 1 and 17 wherein R^4 is other than methylene also solve the technical problem (to show that R^4 = methylene is not an essential feature of the invention).

Industrial applicability

Claims 1-10, 17-24 fulfil the requirements of Article 33(4) PCT.
No unified criteria exist in the PCT Contracting States for assessing whether present claims 11-16, 25-30 are industrially applicable. The patentability can be dependent upon the formulation of the claims. For example, the EPO does not

consider claims to the use of a compound in medical treatment to be industrially applicable, but allows claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

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TRATADO DE COOPERACIÓN DE PATENTES

PCT

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL

(Artículo 36 y Regla 70 del PCT)

Referencia del expediente del agente o solicitante 9/240PCT	**PARA ACTUACIONES ADICIONALES**	Ver notificación de Transmisión del Reporte de Examen Preliminar (Formato PCT/IPEA416)
Solicitud Internacional No. PCT/US03/08901	Fecha de presentación internacional (*día/mes/año*) 21.03.2003	Fecha de prioridad (*día/mes/año*) 26.03.2002
Clasificación Internacional de Patentes (IPC) o clasificación nacional e IPC A61K 31/44		
Solicitante BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.		

1. Este informe de examen preliminar internacional ha sido preparado por esta Administración encargada del Examen Preliminar Internacional y se envía al solicitante en concordancia con el artículo 36.

2. Este **INFORME** consta de una total de 5 hojas, incluyendo la portada

   ☐ Este informe también se acompaña de **ANEXOS**, esto es documentos de la descripción, reivindicaciones y/o dibujos que han sido corregidos y que son la base de este informe y/o documentos que contienen rectificaciones realizadas ante esta Administración (Ver Regla 70.16 y Sección 607 de las Instrucciones Administrativas según el PCT)

   Estos anexos constan de un total de _____ hojas.

3. Este informe contiene indicaciones relativas a los siguientes aspectos:

   I ☒ Fundamentos del Informe

   II ☐ Prioridad

   III ☒ No se establece concepto relativo a la novedad, nivel inventivo y aplicación industrial

   IV ☐ Carencia de unidad de la invención

   V ☒ Declaración razonada según el artículo 35(2), en relación con la novedad, nivel inventivo o aplicación industrial; citaciones y explicaciones que soportan dicha declaración

   VI ☐ Ciertos documentos citados

   VII ☐ Ciertos defectos de la solicitud internacional

   VIII ☐ Ciertas observaciones respecto a la solicitud internacional

Fecha de presentación de la demanda	Fecha de terminación de este reporte
18.09.2003	18.11.2003
Nombre y dirección de correo de la autoridad encargada del examen preliminar Oficina Europea de Patentes D-80298 Munich Tel. +49 89 2399 – 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Funcionario Autorizado Johnson, C. Teléfono No. +49 89 2399 - 8287

I. Base del Informe

1. Respecto a los **elementos** de la solicitud internacional (*Las hojas de reemplazo que han sido entregadas a la Oficina receptora en respuesta a la invitación bajo el Artículo 14 se refieren en este informe como "originalmente presentadas" y no se anexan a este informe ya que ellas no contienen modificaciones (Regla 70.16 y 70.17):*

☒ La descripción:
páginas 1 – 186, como se presentaron originalmente

☒ Las reivindicaciones:
números 1 – 30, como se presentaron originalmente

2. Respecto al **lenguaje**, todos los elementos marcados anteriormente estuvieron disponibles o fueron enviados a la Administración en el lenguaje en que se presentó la solicitud internacional, a menos que se indique otra cosa en este punto.

Estos elementos estuvieron disponibles o fueron enviados a esta Administración en el siguiente lenguaje _____ el cual es:

☐ el lenguaje de la traducción enviada para propósitos de la búsqueda internacional (bajo Regla 23.1 (b)).
☐ el lenguaje de la publicación de la solicitud internacional (bajo Regla 48.3(b)).
☐ el lenguaje de la traducción entregada con propósitos del examen preliminar internacional (bajo Regla 55.2 y/o 55.3).

3. Respecto a cualquier **secuencia de nucleótido y/o amino ácidos** divulgada en la solicitud internacional, el examen preliminar internacional se llevó a cabo con base en el listado de secuencias:

☐ contenido en la solicitud internacional en forma escrita
☐ presentado junto con la solicitud internacional en forma legible por computador
☐ entregado posteriormente a esta Administración en forma legible por computador
☐ La declaración de que el listado de secuencias posteriormente entregado no va más allá de lo divulgado en la solicitud internacional originalmente presentada, ha sido entregada.
☐ La declaración de que la información grabada en la forma legible por computador es idéntica al listado de secuencias escrito que se ha entregado.

4. Las modificaciones han dado como resultado la cancelación de:

☐ la descripción, páginas _____,
☐ las reivindicaciones, Nos. _____,
☐ los dibujos, página _____.

5. ☐ Este reporte ha sido establecido como si (parte de) las modificaciones no se hubieran realizado, ya que éstas han sido consideradas como una ampliación de lo inicialmente divulgado como se indica en la Casilla Suplementaria (Regla 70.2(c)).

(Cualquier hoja de reemplazo que contenga dichas modificaciones deberá ser referida bajo el punto 1 y anexada a este informe.)

6. Observaciones Adicionales, si son necesarias:

III. No establecimiento de opinión con respecto a la novedad, nivel inventivo y aplicabilidad industrial.

1. La pregunta de si la invención reivindicada parece tener novedad, nivel inventivo (que no sea obvia), o que sea aplicable industrialmente no ha sido examinada con respecto a:

☐ la solicitud internacional completa
☒ las reivindicaciones Nos. 1 – 30 (parte),

Porque

☒ la solicitud internacional, o las mencionadas reivindicaciones Nos. 11–16, 25–30 se relacionan con los siguientes objetos, los cuales no requieren examen preliminar internacional *(especifique):*

ver hoja separada

☒ la descripción, las reivindicaciones o los dibujos *(indique los elementos particulares abajo)* o las mencionadas reivindicaciones Nos. 1-14, 16-28, 30 (toda la parte) son demasiado confusas que no se puede formar ninguna opinión significativa *(especifique):*

ver hoja separada

☒ *la descripción, o las mencionadas reivindicaciones* Nos. 1-14, 16-28, 30 (toda la parte) *no están* adecuadamente soportadas por la descripción que no se puede formar ninguna opinión significativa.

☐ no se ha establecido un reporte de búsqueda para las mencionadas reivindicaciones Nos. _____

2. No se pudo realizar un examen preliminar internacional significativo debido a fallas en el listado de nucleótidos y/o aminoácidos para dar cumplimiento con los estándares del Anexo C de las *Instrucciones Administrativas*:

☐ El formato escrito no ha sido suministrado o no cumple con los estándares.

☐ El formato de lectura por computador no ha sido suministrado o no cumple con los estándares.

V. Declaración motivada según el Artículo 35(2) en cuanto a la novedad, el nivel inventivo y la aplicación industrial; citas y explicaciones que apoyan esta declaración.

1. Declaración

Novedad (N)	Reivindicaciones	1 – 30	SI
	Reivindicaciones		NO
Nivel inventivo (NI)	Reivindicaciones	1 – 30	SI
	Reivindicaciones		NO
Aplicación industrial (AI)	Reivindicaciones	1 – 10, 17 - 24	SI
	Reivindicaciones		NO

2. Citas y explicaciones (Regla 70.7)

ver hoja separada

III. No establecimiento de opinión

Las reivindicaciones son consideradas como que no cumplen con los requerimientos del artículo 5 y 6 del PCT por la utilización de la expresión "prodroga" (ver Informe de Búsqueda Internacional para detalles). Por lo tanto las reivindicaciones 1 a 14, 16 a 28 y 30 no han sido buscadas completamente. El siguiente examen ha sido realizado para la materia objeto que ha sido buscada solamente. Las reivindicaciones 11 a 16, 25 a 30 se relacionan con la materia objeto que es considerada por esta Autoridad como que está cubierta por las salvedades de la regla 67.1 (iv) del PCT. En consecuencia, no se va a formular ninguna opinión con relación a la aplicabilidad industrial para la materia objeto de dichas reivindicaciones (articulo 34(4)(a)(i) del PCT).

V. Declaración Motivada

Se hace referencia al siguiente documento:

D1 : US-B-6 323 199

Novedad

La materia objeto de las Reivindicaciones 1 y 17 difiere de la del documento D1 porque no hay un grupo amino que separa el grupo heteroarilo R^5 del grupo R^4. Por lo tanto las reivindicaciones 1 a 30 cumplen con los requerimientos del artículo 33(2) del PCT.

Nivel Inventivo

El documento D1 revela compuestos con afinidad por el receptor glucocorticoide para el uso como agentes antinflamatorios. El problema técnico a resolver por la presente invención parece ser el suministro de compuestos adicionales con esta actividad. En la ausencia de cualquier revelación que muestra que el grupo amino de D1 no es esencial para la actividad biológica, aquellos de los compuestos reivindicados en la presente, que tienen la actividad deseada, pueden ser considerados inventivos. Debe notarse que todos los compuestos ejemplificados parecen tener R^4= metileno. Podría ser necesario en la fase regional de examen proporcionar evidencia que muestre que los compuestos de las reivindicaciones 1 a 17, en donde R^4 es otro que metileno tan bien soluciona el problema técnico (mostrar que R^4 = metileno no es una característica esencial de la invención).

Aplicabilidad Industrial

Las reivindicaciones 1 a 10, 17 a 24 cumplen con los requerimientos del articulo 33(4) del PCT.

No existe un criterio unificado entre los Estados Contratantes del PCT para evaluar si llas presentes reivindicaciones 11 a 16, 25 a 30 tiene aplicabilidad industrial. Por ejemplo, la OPE no tiene en consideración reivindicaciones para el uso de un compuesto en el tratamiento medico para ser industrialmente aplicable, pero permite reivindicaciones dirigidas a un compuesto conocido para la manifactura de un medicamento para un tratamiento medico nuevo.

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MIMÉTICOS DE GLUCOCORTICOIDES, PROCEDIMIENTOS PARA SU PREPARACIÓN, COMPOSICIONES FARMACÉUTICAS Y USOS DE LOS MISMOS

Campo de la invención

La presente invención se refiere a miméticos de glucocorticoides o ligandos, a procedimientos para preparar dichos compuestos, a su uso en composiciones farmacéuticas y a su uso para modular la función de los receptores de glucocorticoides, tratar estados de enfermedad y trastornos mediados por la función del receptor de glucocorticoides en un paciente que necesita dicho tratamiento y a otros usos.

Antecedentes de la invención

Los glucocorticoides, una clase de esteroides, son hormonas endógenas con profundos efectos sobre el sistema inmunitario y varios sistemas de órganos. Éstos suprimen una diversidad de funciones inmunitarias e inflamatorias mediante inhibición de citoquinas inflamatorias tales como IL-1, IL-2, IL-6 y TNF, inhibición de metabolitos del ácido araquidónico incluyendo prostaglandinas y leucotrienos, agotamiento de los linfocitos T y reducción de la expresión de moléculas de adhesión en células endoteliales (P.J. Barnes, Clin. Sci., 1998, 94, págs. 557-572; P.J. Barnes *et al.*, Trends Pharmacol. Sci., 1993, 14, págs. 436-441). Además de estos efectos, los glucocorticoides estimulan la producción de glucosa en el hígado y el catabolismo de proteínas, desempeñan una función en el equilibrio de electrolitos y agua, reducen la absorción de calcio e inhiben la función de los osteoblastos.

Las actividades de supresión antiinflamatorias e inmunes de glucocorticoides endógenos ha estimulado el desarrollo de derivados de glucocorticoides sintéticos que incluyen dexametasona, prednisona y prednisolona (L. Parente, Glucocorticoids, N.J. Goulding and R.J. Flowers (eds.), Boston: Birkhauser, 2001, págs. 35-54). Estos han encontrado un uso extendido en el tratamiento de trastornos inflamatorios, inmunes y alérgicos, incluyendo enfermedades reumáticas tales como la artritis reumatoide, artritis juvenil y espondilitis anquilosante, enfermedades dermatológicas incluyendo psoriasis y pénfigo, trastornos alérgicos incluyendo rinitis alérgica, dermatitis atópica y dermatitis por contacto, estados pulmonares incluyendo asma y enfermedad pulmonar obstructiva crónica (EPOC) y otras enfermedades inmunes e inflamatorias incluyendo enfermedad de Crohn, colitis ulcerosa, lupus eritematoso sistémico, hepatitis activa crónica autoinmune, osteoartritis, tendonitis y bursitis (J. Toogood, Glucocorticoids, N.J. Goulding and R.J. Flowers (eds.), Boston: Birkhauser, 2001, págs. 161-174). También

se han usado para ayudar a prevenir el rechazo en el trasplante de órganos.

Desafortunadamente, además de los efectos terapéuticos deseados de los glucocorticoides, su uso se asocia con una serie de efectos secundarios adversos, algunos de los cuales pueden severos y amenazar la vida del paciente. Estos incluyen alteraciones en el balance de fluidos y electrolitos, edema, aumento de peso, hipertensión, debilidad muscular, desarrollo o empeoramiento de diabetes mellitus y osteoporosis. Por tanto, un compuesto que presente un perfil reducido de efectos secundarios manteniendo los potentes efectos antiinflamatorios sería particularmente deseable, en especial, cuando se trate una enfermedad crónica.

Los efectos de los glucocorticoides están mediados a nivel celular por el receptor de glucocorticoides (R.H. Oakley and J. Cidlowski, Glucocorticoids, N.J. Goulding and R.J. Flowers (eds.), Boston: Birkhauser, 2001, págs. 55-80). El receptor de glucocorticoides es un miembro de una clase de receptores intracelulares estructuralmente relacionados que, cuando se acoplan a un ligando pueden funcionar como un factor de transcripción que afecta a la expresión génica (R.M. Evans, Science, 1988, 240, págs. 889-895). Otros miembros de la familia de receptores de esteroides incluyen los mineralocorticoides, progesterona, estrógenos y receptores de estrógenos. Además de los efectos mencionados antes para los glucocorticoides, las hormonas que actúan sobre esta familia de receptores tiene una marcada influencia en la homeostasis corporal, el metabolismo mineral, la respuesta al estrés y el desarrollo de las características sexuales. Glucocorticoids, N.J. Goulding and R.J. Flowers (eds.), Boston: Birkhauser, 2001, se incorpora como referencia en la presente memoria en su totalidad para describir mejor el estado de la técnica.

Se ha propuesto un mecanismo molecular que apoya los efectos beneficiosos antiinflamatorios y los efectos secundarios indeseados (por ejemplo, S. Heck *et al.*, EMBO J, 1994, 17, págs. 4087-4095; H.M. Reichardt *et al.*, Cell, 1998, 93, págs. 531-541; F. Tronche *et al.*, Curr. Opin. in Genetics and Dev., 1998, 8, págs. 532-538). Muchos de los efectos secundarios metabólicos y cardiovasculares se cree que son el resultado de un proceso denominado transactivación. En la transactivación, la translocación a los núcleos del receptor de glucocorticoides unido a ligando va seguida por la unión a elementos de respuesta a glucocorticoides (GRE) en la región del promotor de los genes asociados a los efectos secundarios, por ejemplo, fosfoenolpiruvato carboxi quinasa (PEPCK), en el caso de la producción de glucosa. El resultado es una mayor velocidad de transcripción de estos genes que se cree que

origina finalmente los efectos secundarios observados. Los efectos antiinflamatorios se cree que son debidos a un proceso denominado transrrepresión. En general, la transrrepresión es un proceso independiente de unión de ADN que se origina por la inhibición de las vías mediadas por NK-kB y AP-1, conduciendo a la regulación a niveles inferiores de muchos mediadores inflamatorios e inmunes. Además, se cree que una serie de los efectos secundarios observados puede deberse a la reactividad cruzada de los glucocorticoides disponibles normalmente con otros receptores de esteroides, en particular, los receptores de mineralocorticoides y progesterona.

Así, puede ser posible descubrir ligandos para el receptor de glucocorticoides que son muy selectivos y, al unirse, pueden disociar las vías de transactivación y transrrepresión, proporcionando agentes terapéuticos con un perfil reducido de efectos secundarios. Se han descrito los sistemas de ensayo para determinar los efectos sobre la transactivación y transrrepresión (por ejemplo, C.M. Bamberger and H.M. Schulte, Eur. J. Clin. Invest., 2000, 30 (suppl. 3), págs. 6-9). La selectividad por el receptor de glucocorticoides se puede determinar comparando la afinidad de unión por este receptor con la de otros receptores de la familia de los esteroides incluyendo los citados antes.

Los glucocorticoides también estimulan la producción de glucosa en el hígado mediante un proceso denominado glucogenolisis y se cree que este proceso está mediado por sucesos de transactivación. Una mayor producción de glucosa puede exacerbar la diabetes tipo II, por tanto, un compuesto que inhiba de forma selectiva la producción de glucosa mediada por glucocorticoides puede tener utilidad terapéutica en esta indicación (J.E. Freidman *et al.*, J. Biol. Chem., 1997, 272, págs. 31475-31481).

Se han descrito en la bibliografía de patentes y científica nuevos ligandos para el receptor de glucocorticoides. Por ejemplo, la publicación internacional PCT nº WO 99/33786 describe compuestos de trifenilpropanamida con uso posible en el tratamiento de enfermedades inflamatorias. La publicación internacional PCT nº WO 00/66522 describe compuestos no esteroideos como moduladores selectivos del receptor de glucocorticoides, potencialmente útiles en el tratamiento de enfermedades metabólicas e inflamatorias. La publicación internacional PCT nº WO 99/41256 describe moduladores tetracíclicos del receptor de glucocorticoides potencialmente útiles para tratar enfermedades inmunes, autoinmunes e inflamatorias. La patente de Estados Unidos nº 5.688.810 describe diversos compuestos no esteroideos como moduladores de los receptores de glucocorticoides y otros receptores de esteroides. La publicación internacional PCT nº WO 99/63976 describe un antagonista de glucocorticoides

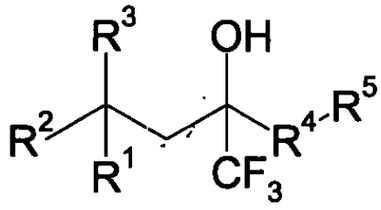
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selectivo en el hígado potencialmente útil en el tratamiento de diabetes. La publicación internacional PCT nº WO 00/32584 describe compuestos no esteroideos que tienen actividad antiinflamatoria con disociación entre efectos antiinflamatorios y metabólicos. La publicación internacional PCT nº WO 98/54159 describe acilanilidas no esteroideas cíclicamente sustituidas con actividad mixta gestágeno y andrógeno. La patente de Estados Unidos nº 4.880.839 describe acilanilidas que tienen actividad progestacional y el documento EP 253503 describe acilanilidas con propiedades antiandrógenos. La publicación internacional PCT nº WO 97/27852 describe amidas que son inhibidoras de la farnesil-proteína transferasa.

Un compuesto que se encuentre que interaccione con el receptor de glucocorticoides en un ensayo de unión podría ser un agonista o un antagonista. Las propiedades como agonista del compuesto se podrían evaluar en los ensayos de transactivación o transrrepresión descritos antes. Dada la eficacia demostrada por los fármacos glucocorticoides disponibles en enfermedades inflamatorias e inmunes y sus efectos secundarios adversos, sigue existiendo la necesidad de nuevos agonistas del receptor de glucocorticoides con selectividad sobre otros miembros de la familia de receptores de esteroides y una disociación de las actividades de transactivación y transrrepresión. Como alternativa, se puede encontrar que el compuesto tiene actividad antagonista. La mayor producción de glucosa inducida por el exceso de glucocorticoides puede exacerbar la diabetes existente o desencadenar una diabetes latente. Así, un ligando para un receptor de glucocorticoides que se encuentre que sea un antagonista puede ser útil, *inter alia*, para tratar o prevenir la diabetes.

Sumario de la invención

La presente invención se refiere a compuestos de Fórmula (IA)



(IA)

en la que:

R^1 es un grupo arilo o heteroarilo, cada uno opcionalmente sustituido con uno a tres grupos sustituyentes,

siendo cada grupo sustituyente de R^1 independientemente alquilo C_1-C_5, alquenilo C_2-C_5, alquinilo C_2-C_5, cicloalquilo C_3-C_8, heterociclilo, arilo,

heteroarilo, alcoxi C_1-C_5, alqueniloxi C_2-C_5, alquiniloxi C_2-C_5, ariloxi, acilo, alcoxicarbonilo C_1-C_5, alcanoiloxi C_1-C_5, alcanoilo C_1-C_5, aroilo, aminocarbonilo, alquilaminocarbonilo, dialquilaminocarbonilo, aminocarboniloxi, (alquil C_1-C_5)aminocarboniloxi, di(alquil C_1-C_5)aminocarboniloxi, (alcanoil C_1-C_5)amino, (alcoxi C_1-C_5)carbonilamino, (alquil C_1-C_5)sulfonilamino, aminosulfonilo, (alquil C_1-C_5)aminosulfonilo, di(alquil C_1-C_5)aminosulfonilo, halógeno, hidroxi, carboxi, ciano, trifluorometilo, trifluorometoxi, nitro o amino, estando el átomo de nitrógeno opcionalmente mono- o disustituido independientemente con alquilo C_1-C_5 o arilo; o ureido, estando cualquier átomo de nitrógeno opcionalmente sustituido independientemente con alquilo C_1-C_5; o (alquil C_1-C_5)tio, en el que el átomo de azufre está opcionalmente oxidado a un sulfóxido o sulfona,

estando cada grupo sustituyente de R^1 opcionalmente sustituido independientemente con uno a tres grupos sustituyentes seleccionados de metilo, metoxi, halógeno, hidroxi, oxo, ciano o amino,

R^2 y R^3 son cada uno independientemente hidrógeno o alquilo C_1-C_5, o R^2 y R^3 junto con el átomo de carbono al que están unidos en común forman un anillo espiro cicloalquilo C_3-C_8;

R^4 es alquilo C_1-C_5, alquenilo C_2-C_5 o alquinilo C_2-C_5, cada uno opcionalmente sustituido independientemente con uno a tres grupos sustituyentes,

siendo cada grupo sustituyente de R^4 independientemente alquilo C_1-C_3, hidroxi, halógeno, amino u oxo; y

R^5 es un grupo heteroarilo opcionalmente sustituido independientemente con uno a tres grupos sustituyentes,

siendo cada grupo sustituyente de R^5 independientemente alquilo C_1-C_5, alquenilo C_2-C_5, alquinilo C_2-C_5, cicloalquilo C_3-C_8, heterociclilo, arilo, heteroarilo, alcoxi C_1-C_5, alqueniloxi C_2-C_5, alquiniloxi C_2-C_5, ariloxi, acilo, (alcoxi C_1-C_5)carbonilo, alcanoiloxi C_1-C_5, aminocarbonilo, alquilaminocarbonilo, dialquilaminocarbonilo, aminocarboniloxi, (alquil C_1-C_5)aminocarboniloxi, di(alquil C_1-C_5)aminocarboniloxi, (alcanoil C_1-C_5)amino, (alcoxi C_1-C_5)carbonilamino, (alquil C_1-C_5)sulfonilamino, aminosulfonilo,

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(alquil C_1-C_5)aminosulfonilo, di(alquil C_1-C_5)aminosulfonilo, halógeno, hidroxi, carboxi, ciano, trifluorometilo, trifluorometoxi, trifluorometiltio, nitro o amino, estando el átomo de nitrógeno opcionalmente mono- o disustituido independientemente con alquilo C_1-C_5; o ureido en el que el átomo de nitrógeno está opcionalmente sustituido independientemente con alquilo C_1-C_5; o (alquil C_1-C_5)tio, en el que el átomo de azufre está opcionalmente oxidado a un sulfóxido o sulfona,

estando cada grupo sustituyente de R^5 opcionalmente sustituido independientemente con uno a tres grupos sustituyentes seleccionados de alquilo C_1-C_3, alcoxi C_1-C_3, halógeno, hidroxi, oxo, ciano, amino o trifluorometilo,

o uno de sus tautómeros, profármacos, solvatos o sales.

Otro aspecto de la invención incluye compuestos de Fórmula (IA), en la que:

R^1 es tienilo, fenilo, naftilo, dihidrobenzofuranilo, benzofuranilo, cromanilo, dihidroindolilo, indolilo, dihidrobenzotienilo, benzotienilo, benzodioxolanilo, dihidrobenzoxazolilo, benzoxazolilo, bencisoxazolilo, benzopirazolilo, bencimidazolilo, quinolinilo, piridinilo, pirimidinilo o pirazinilo, cada uno opcionalmente sustituido independientemente con uno a tres grupos sustituyentes,

siendo cada grupo sustituyente de R^1 independientemente alquilo C_1-C_3, alquenilo C_2-C_3, alquinilo C_2-C_3, alcoxi C_1-C_3, alqueniloxi C_2-C_3, alcanoilo C_1-C_3, alcoxicarbonilo C_1-C_3 , alcanoiloxi C_1-C_3 , halógeno, hidroxi, carboxi, ciano, trifluorometilo, trifluorometoxi, nitro o (alquil C_1-C_3)tio, en el que el átomo de azufre está opcionalmente oxidado a un a sulfóxido o sulfona,

estando cada grupo sustituyente de R^1 opcionalmente sustituido independientemente con un grupo sustituyente seleccionado de metilo, metoxi, halógeno, hidroxi, oxo, ciano o amino;

R^2 y R^3 son cada uno independientemente hidrógeno o alquilo C_1-C_3, o R^2 y R^3 junto con el átomo de carbono al que están unidos en común forman un anillo espiro cicloalquilo C_3-C_6;

R^4 es CH_2; y

R^5 es un grupo imidazolilo, piridilo, indolilo, azaindolilo, diazaindolilo, benzofuranilo, furanopiridinilo, furanopirimidinilo, benzotienilo, tienopiridinilo, tienopirimidinilo, benzoxazolilo, oxazolopiridinilo, benzotiazolilo, tiazolopiridinilo, bencimidazolilo, imidazolopiridinilo, quinolinilo o isoquinolinilo, cada uno opcionalmente sustituido independientemente con uno a tres grupos sustituyentes,

siendo cada grupo sustituyente de R^5 independientemente alquilo C_1-C_3, alquenilo C_2-C_3, fenilo, alcoxi C_1-C_3, metoxicarbonilo, aminocarbonilo, (alquil C_1-C_3)aminocarbonilo, di(alquil C_1-C_3)aminocarbonilo, heterociclilcarbonilo, fluoro, cloro, bromo, ciano, trifluorometilo o alquil C_1-C_3tio, en el que el átomo de azufre está opcionalmente oxidado a un sulfóxido o sulfona,

estando cada grupo sustituyente de R^5 opcionalmente sustituido independientemente con un grupo sustituyente seleccionado de metilo, metoxi, fluoro, cloro, bromo, oxo o trifluorometilo,

o uno de sus tautómeros, profármacos, solvatos o sales.

Otro aspecto más de la invención incluye compuestos Fórmula (IA), en la que:

R^1 es tienilo, fenilo, naftilo, piridilo, cromanilo, dihidrobenzofuranilo o benzofuranilo, cada uno opcionalmente sustituido independientemente con uno o dos grupos sustituyentes,

siendo cada grupo sustituyente de R^1 independientemente metilo, etilo, metoxi, etoxi, fluoro, cloro, bromo, hidroxi, trifluorometilo, trifluorometoxi o ciano;

R^2 y R^3 son cada uno independientemente metilo, o R^2 y R^3 junto con el átomo de carbono al que están unidos en común forman un anillo espirociclopropilo;

R^4 es CH_2; y

R^5 es un grupo piridilo, indolilo, azaindolilo, benzofuranilo, furanopiridinilo, tienopiridinilo, benzoxazolilo, bencimidazolilo, quinolinilo o isoquinolinilo, cada

uno opcionalmente sustituido independientemente con uno a tres grupos sustituyentes,

siendo cada grupo sustituyente de R^5 independientemente metilo, fenilo, metoxicarbonilo, aminocarbonilo, metilaminocarbonilo, dimetilaminocarbonilo, morfolinilcarbonilo, fluoro, cloro, bromo, ciano o trifluorometilo,

o uno de sus tautómeros, profármacos, solvatos o sales.

Otro aspecto más de la invención incluye compuestos de Fórmula (IA), en la que:

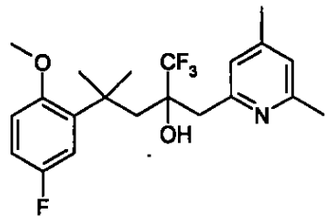
R^1 es fenilo, dihidrobenzofuranilo o benzofuranilo, cada uno opcionalmente sustituido independientemente con uno a tres grupos sustituyentes,

siendo cada grupo sustituyente de R^1 independientemente alquilo C_1-C_3, alquenilo C_2-C_3, alquinilo C_2-C_3, alcoxi C_1-C_3, alqueniloxi C_2-C_3, alcanoilo C_1-C_3, (alcoxi C_1-C_3)carbonilo, alcanoiloxi C_1-C_3, halógeno, hidroxi, carboxi, ciano, trifluorometilo, nitro o (alquil C_1-C_3)tio, en el que el átomo de azufre está opcionalmente oxidado a un sulfóxido o sulfona; y

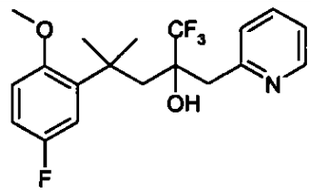
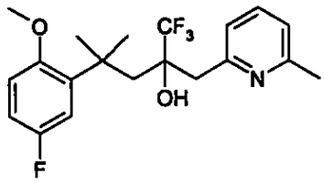
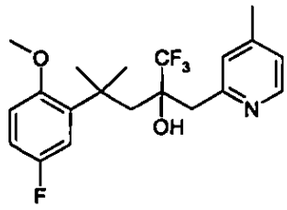
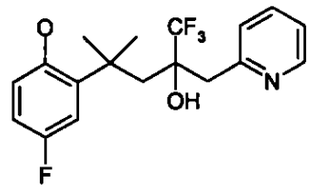
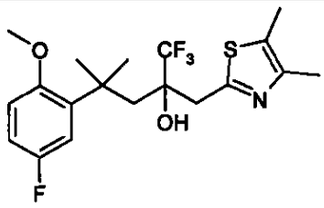
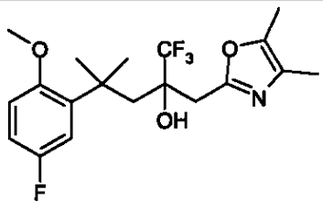
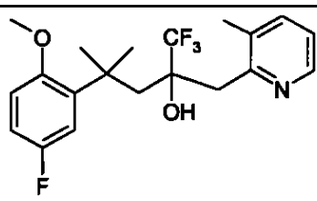
R^2 y R^3 son cada no independientemente hidrógeno o alquilo C_1-C_3,

o uno de sus tautómeros, profármacos, solvatos o sales.

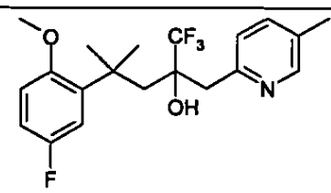
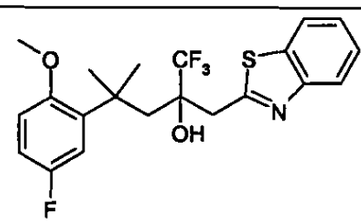
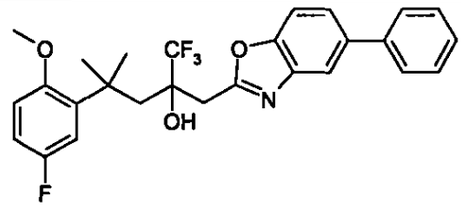
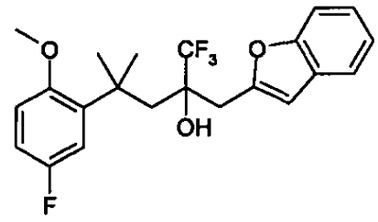
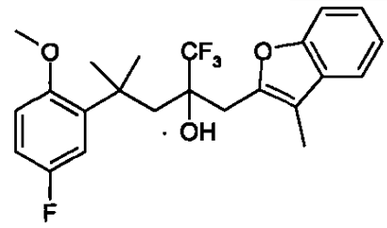
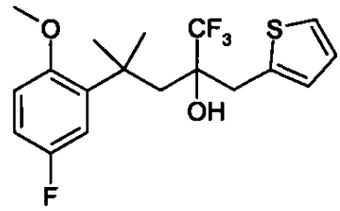
Los siguientes compuestos son representativos de la Fórmula (IA) conforme a la invención:

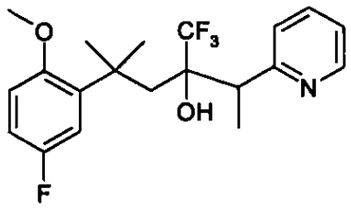
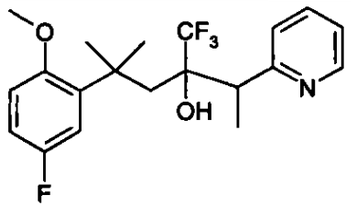
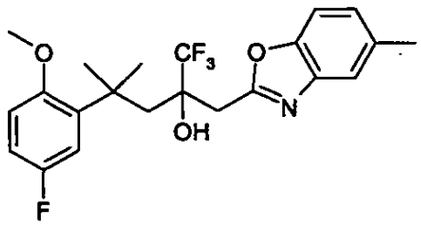
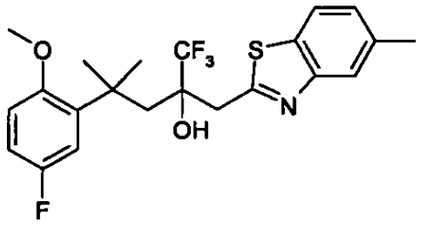
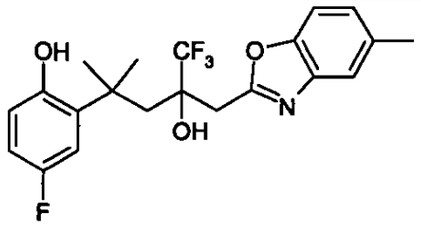
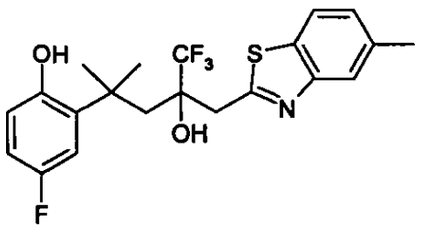
Nombre del compuesto	Estructura del compuesto
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-(4,6-dimetilpiridin-2-ilmetil)-4-metilpentan-2-ol	

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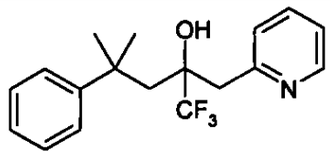
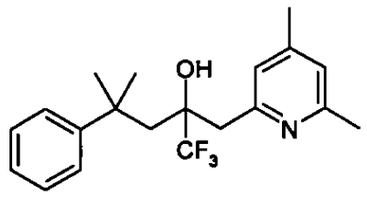
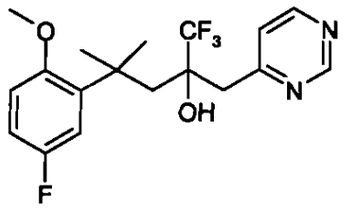
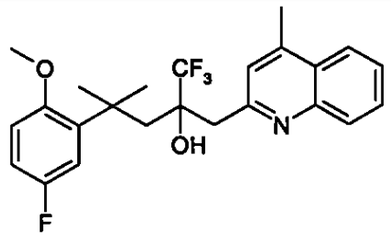
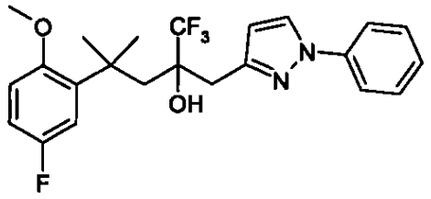
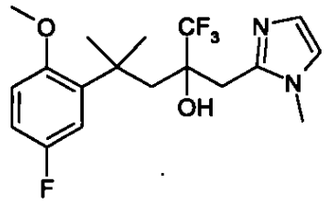
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-(piridin-2-ilmetil)-4-metilpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(6-metilpiridin-2-ilmetil)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(4-metilpiridin-2-ilmetil)pentan-2-ol	
4-Fluoro-2-(4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-piridin-2-ilmetilbutil)fenol	
2-(4,5-Dimetiltiazol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol	
2-(4,5-Dimetiloxazol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(3-metilpiridin-2-ilmetil)pentan-2-ol	

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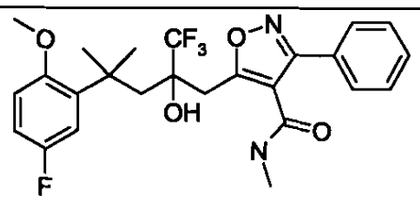
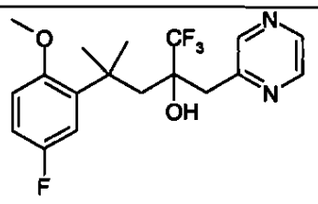
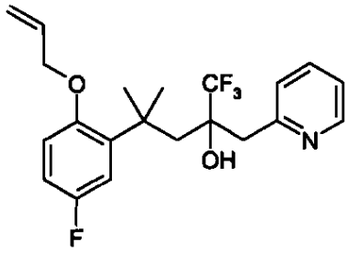
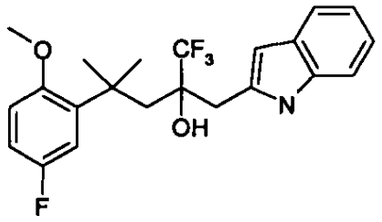
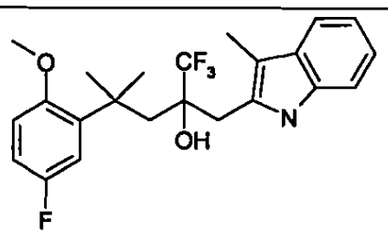
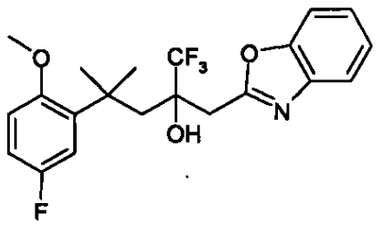
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(5-metilpiridin-2-ilmetil)pentan-2-ol	
2-Benzotiazol-2-ilmetil-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(5-fenilbenzoxazol-2-ilmetil)pentan-2-ol	
2-Benzofuran-2-ilmetil-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(3-metilbenzofuran-2-ilmetil)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-tiofen-2-ilmetilpentan-2-ol	

5-(5-Fluoro-2-metoxifenil)-5-metil-2-piridin-2-il-3-trifluorometilhexan-3-ol	
5-(5-Fluoro-2-metoxifenil)-5-metil-2-piridin-2-il-3-trifluorometilhexan-3-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(5-metilbenzooxazol-2-ilmetil)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(5-metilbenzotiazol-2-ilmetil)pentan-2-ol	
4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(5-metilbenzooxazol-2-ilmetil)butil]fenol	
4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(5-metilbenzotiazol-2-ilmetil)butil]fenol	

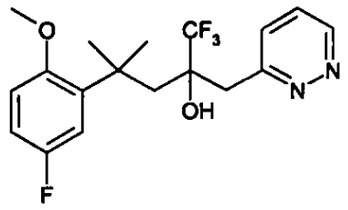
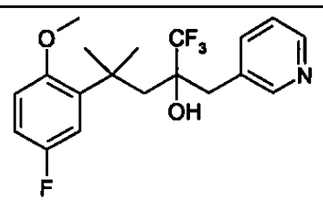
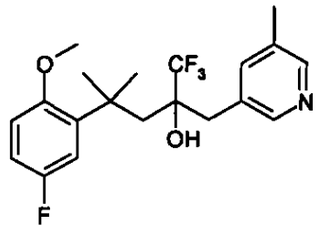
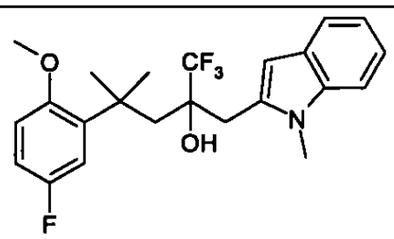
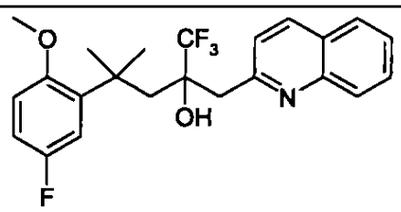
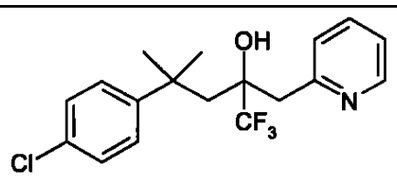
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1,1,1-Trifluoro-4-metil-4-fenil-2-piridin-2-ilmetilpentan-2-ol	
2-(4,6-Dimetilpiridin-2-ilmetil)-1,1,1-trifluoro-4-metil-4-fenilpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-pirimidin-4-ilmetilpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(4-metilquinolin-2-ilmetil)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1-fenil-1*H*-pirazol-3-ilmetil)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1-metil-1*H*-imidazol-2-ilmetil)pentan-2-ol	

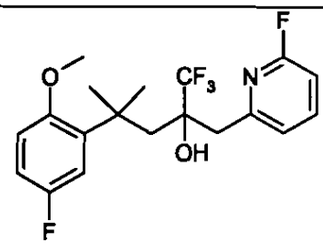
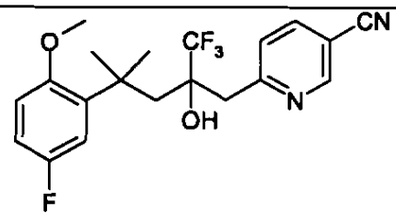
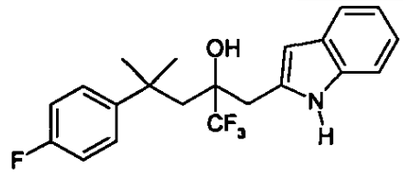
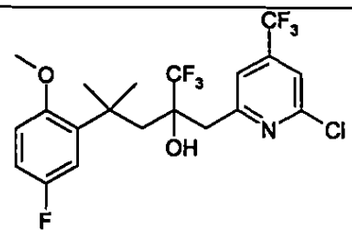
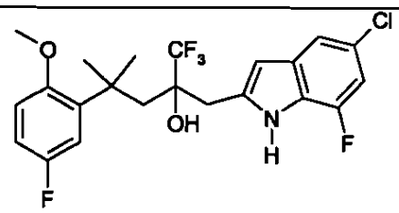
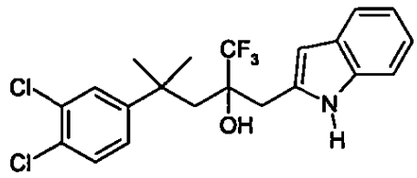
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Metilamida del ácido 5-[4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-3-fenilisoxazol-4-carboxílico	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-pirazin-2-ilmetilpentan-2-ol	
4-(2-Aliloxi-5-fluorofenil)-1,1,1-trifluoro-4-metil-2-piridin-2-ilmetilpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(3-metil-1*H*-indol-2-ilmetil)pentan-2-ol	
2-Benzooxazol-2-ilmetil-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol	

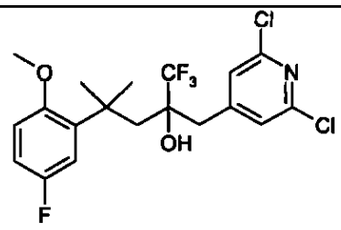
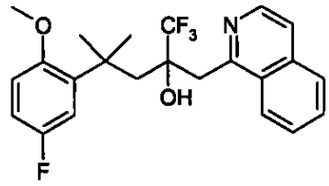
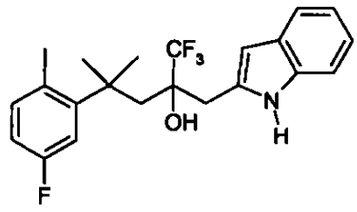
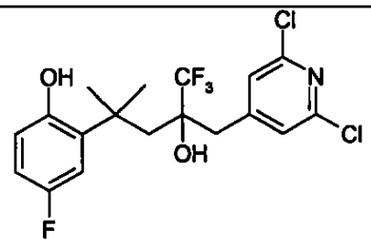
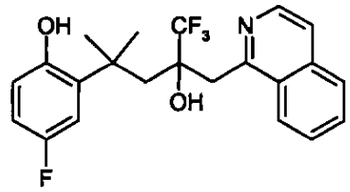
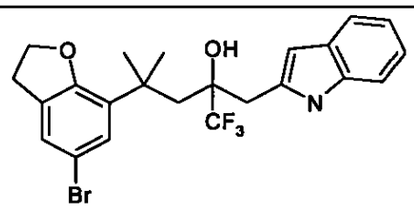
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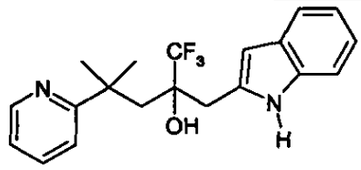
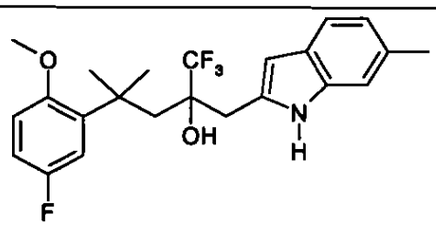
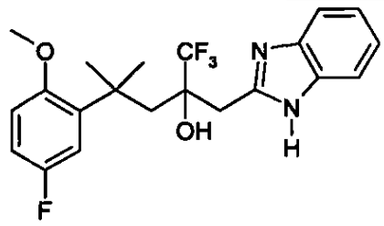
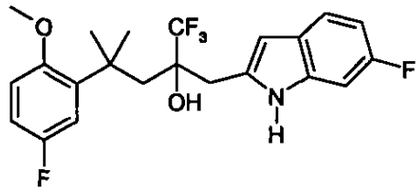
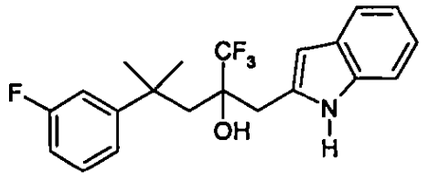
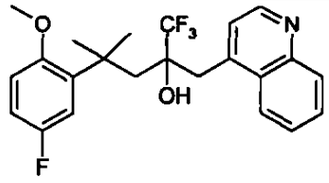
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1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-piridin-3-ilmetilpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(5-metilpiridin-3-ilmetil)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1-metil-1*H*-indol-2-ilmetil)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-quinolin-2-ilmetilpentan-2-ol	
4-(4-Clorofenil)-1,1,1-trifluoro-4-metil-2-piridin-2-ilmetilpentan-2-ol	

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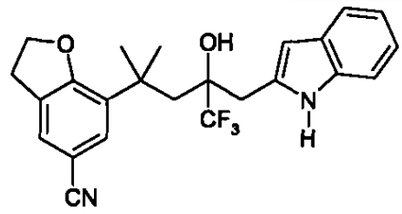
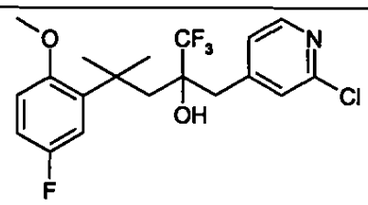
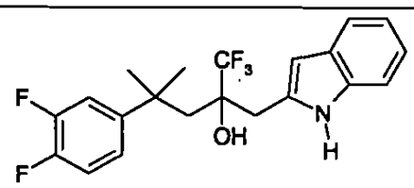
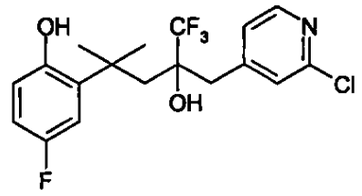
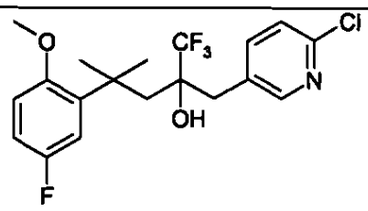
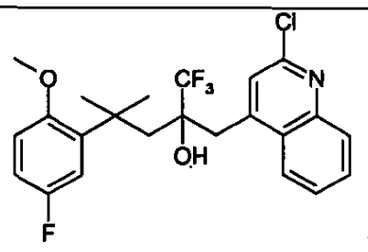
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-(6-fluoropiridin-2-ilmetil)-4-metilpentan-2-ol	
6-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]nicotinonitrilo	
2-(1*H*-Indol-2-ilmetil)-1,1,1-trifluoro-4-(4-fluorofenil)-4-metilpentan-2-ol	
2-(6-Cloro-4-trifluorometilpiridin-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol	
2-(5-Cloro-7-fluoro-1*H*-indol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol	
4-(3,4-Diclorofenil)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol	

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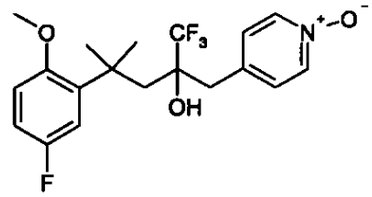
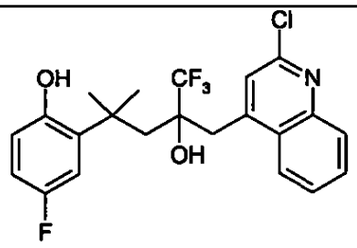
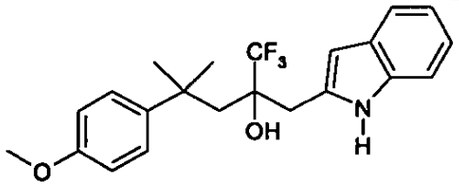
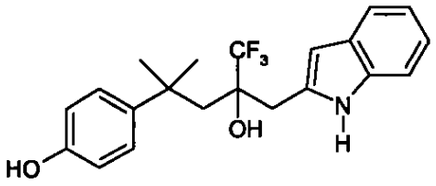
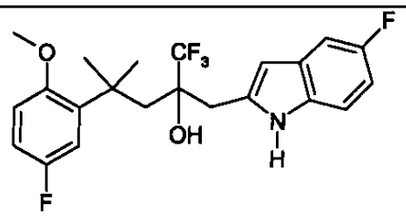
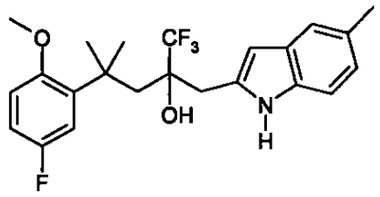
2-(2,6-Dicloropiridin-4-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-isoquinolin-1-ilmetil-4-metilpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol	
2-[3-(2,6-Dicloropiridin-4-ilmetil)-4,4,4-trifluoro-3-hidroxi-1,1-dimetilbutil]-4-fluorofenol	
4-Fluoro-2-(4,4,4-trifluoro-3-hidroxi-3-isoquinolin-1-ilmetil-1,1-dimetilbutil)fenol	
4-(5-Bromo-2,3-dihidrobenzofuran-7-il)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol	

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-piridin-2-ilpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(6-metil-1*H*-indol-2-ilmetil)pentan-2-ol	
2-(1*H*-Bencimidazol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol	
1,1,1-Trifluoro-2-(6-fluoro-1*H*-indol-2-ilmetil)-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol	
1,1,1-Trifluoro-4-(3-fluorofenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(quinolin-4-ilmetil)pentan-2-ol	

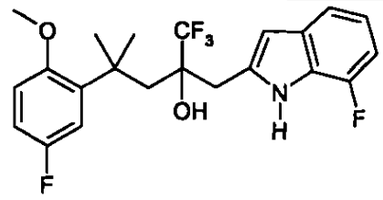
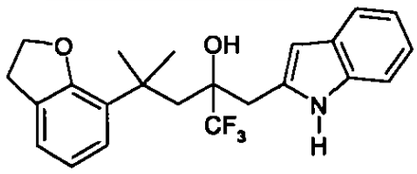
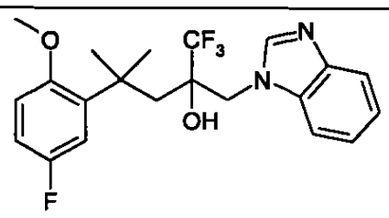
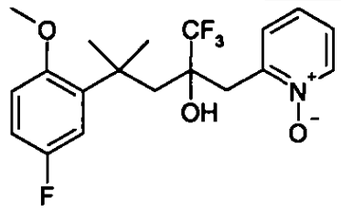
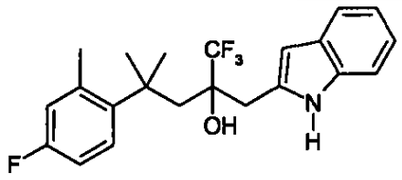
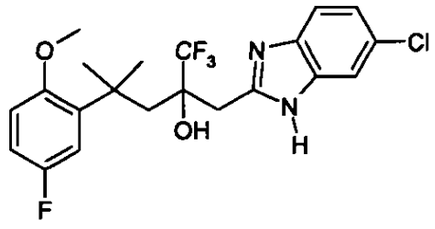
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4-(2,3-dihidro-5-cianobenzofuran-7-il)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(2-cloropiridin-4-ilmetil)pentan-2-ol	
4-(3,4-Difluorofenil)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-hidroxifenil)-4-metil-2-(2-cloropiridin-4-ilmetil)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(2-cloropiridin-5-ilmetil)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(2-cloroquinolin-4-ilmetil)pentan-2-ol	

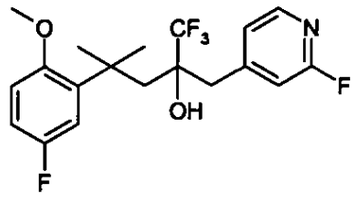
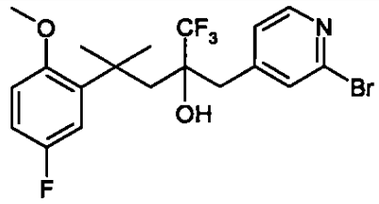
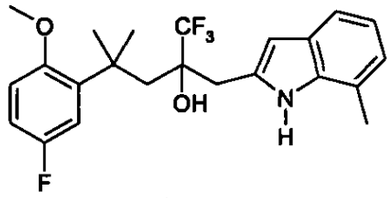
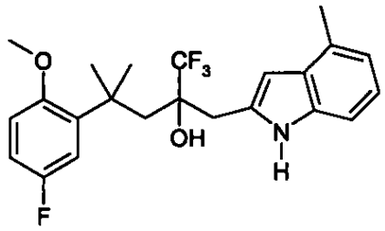
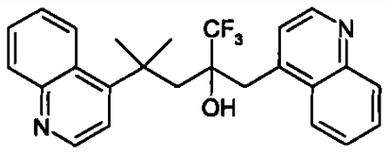
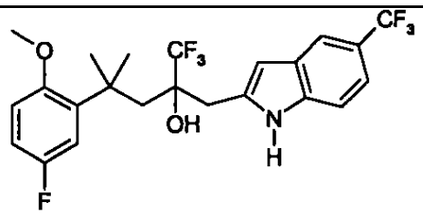
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1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1-oxipiridin-4-ilmetil)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-hidroxifenil)-4-metil-2-(2-cloroquinolin-4-ilmetil)pentan-2-ol	
1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-(4-metoxifenil)-4-metilpentan-2-ol	
4-[4,4,4-Trifluoro-3-hidroxi-3-(1*H*-indol-2-ilmetil)-1,1-dimetilbutil]fenol	
1,1,1-Trifluoro-2-(5-fluoro-1*H*-indol-2-ilmetil)-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol	
1,1,1-Trifluoro-2-(5-metil-1*H*-indol-2-ilmetil)-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol	

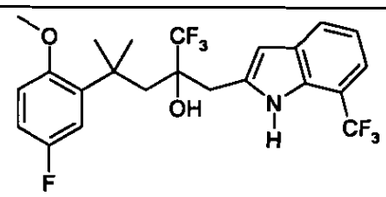
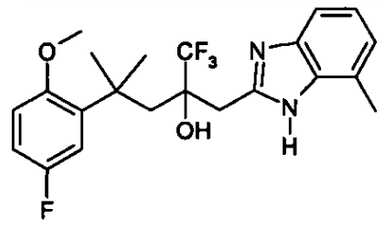
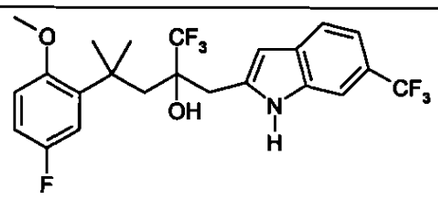
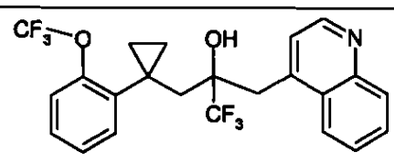
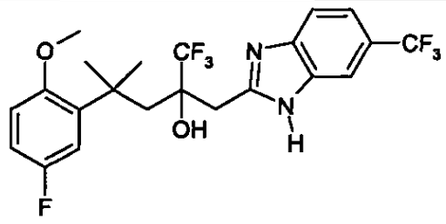
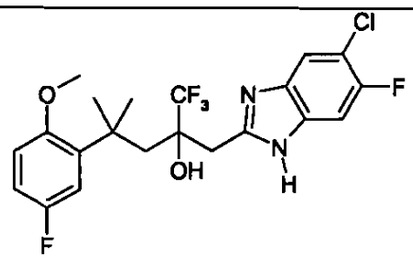
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1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol	
4-(2,3-dihidrobenzofuran-7-il)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol	
2-Bencimidazol-1-ilmetil-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1-oxipiridin-2-ilmetil)pentan-2-ol	
1,1,1-Trifluoro-4-(4-fluoro-2-metilfenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(6-clorobencimidazol-2-ilmetil)pentan-2-ol	

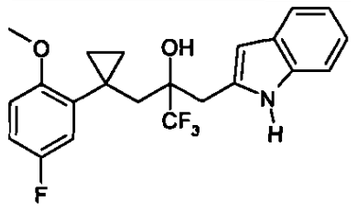
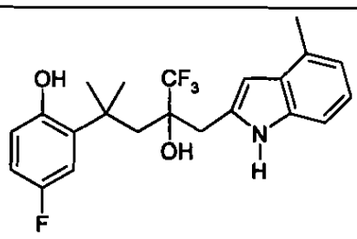
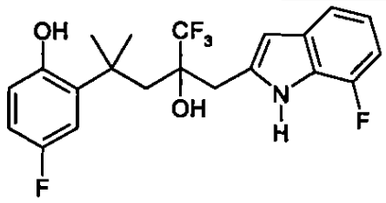
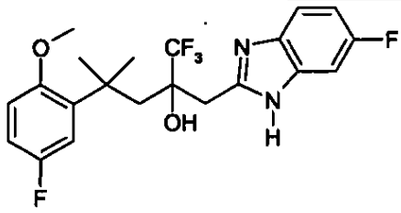
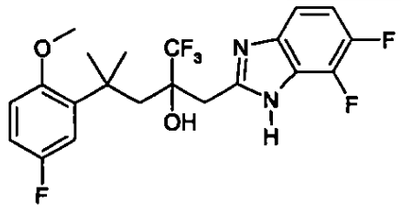
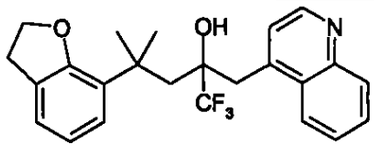
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1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(2-fluoropiridin-4-ilmetil)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(2-bromopiridin-4-ilmetil)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(7-metil-1*H*-indol-2-ilmetil)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(4-metil-1*H*-indol-2-ilmetil)pentan-2-ol	
1,1,1-Trifluoro-4-metil-4-quinolin-4-il-2-quinolin-4-ilmetilpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(5-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol	

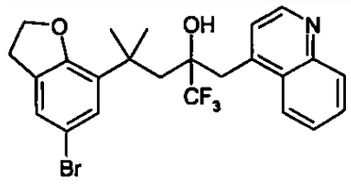
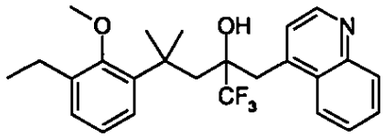
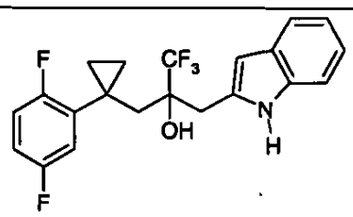
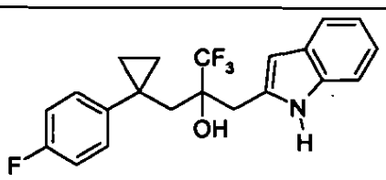
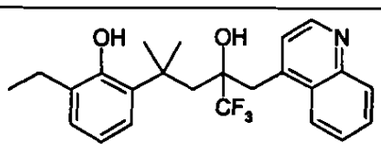
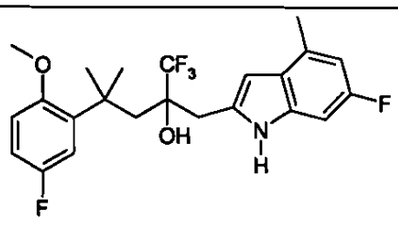
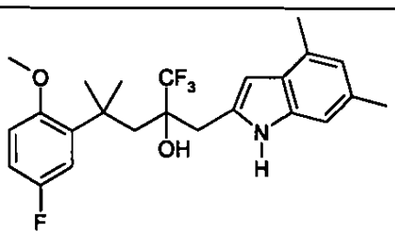
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1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(7-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(7-metil-1*H*-benzoimidazol-2-ilmetil)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(6-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol	
1,1,1-Trifluoro-2-quinolin-4-ilmetil-3-[1-(2-trifluorometoxifenil)ciclopropil]propan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(6-trifluorometil-1*H*-benzoimidazol-2-ilmetil)pentan-2-ol	
2-(5-Cloro-6-fluoro-1*H*-benzoimidazol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol	

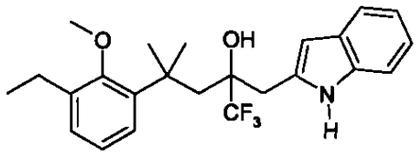
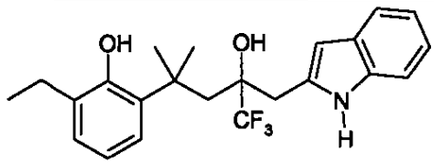
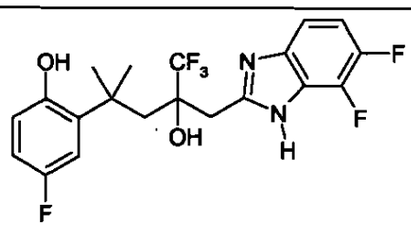
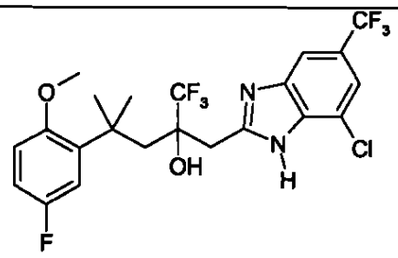
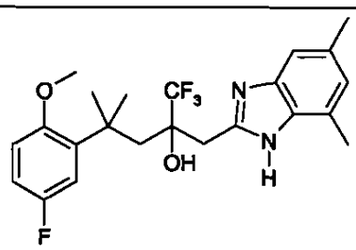
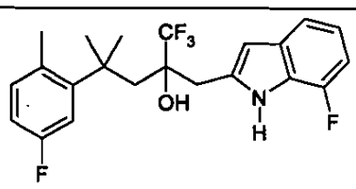
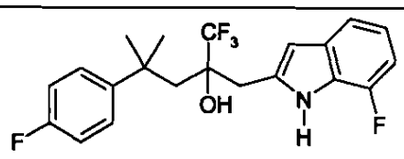
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1,1,1-Trifluoro-3-[1-(5-fluoro-2-metoxifenil)ciclopropil]-2-(1*H*-indol-2-ilmetil)propan-2-ol	
4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(4-metil-1*H*-indol-2-ilmetil)butil]fenol	
4-Fluoro-2-[4,4,4-trifluoro-3-(7-fluoro-1*H*-indol-2-ilmetil)-3-hidroxi-1,1-dimetilbutil]fenol	
1,1,1-Trifluoro-2-(6-fluoro-1*H*-benzoimidazol-2-ilmetil)-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol	
2-(6,7-Difluoro-1*H*-benzoimidazol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol	
4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol	

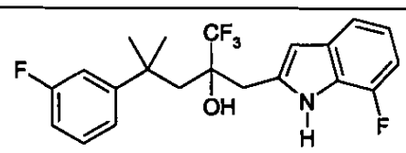
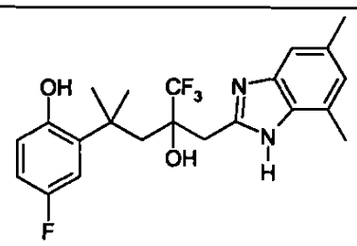
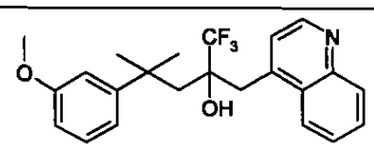
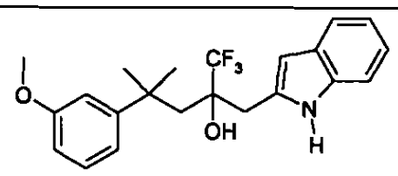
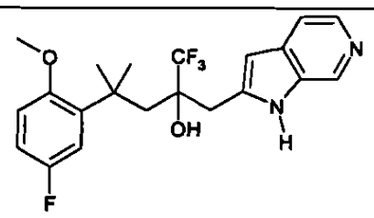
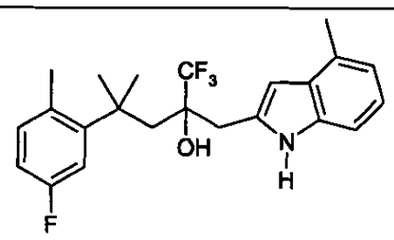
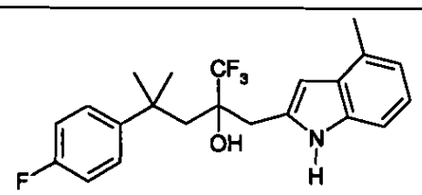
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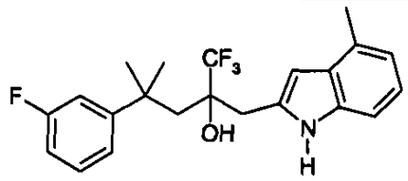
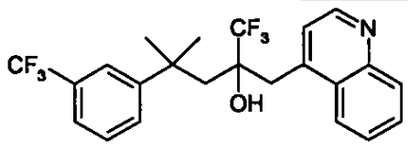
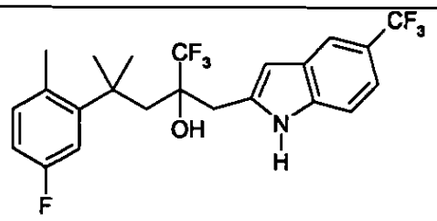
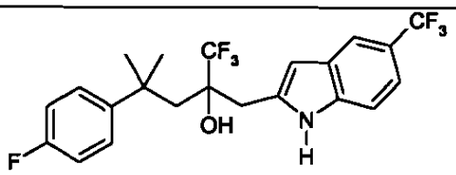
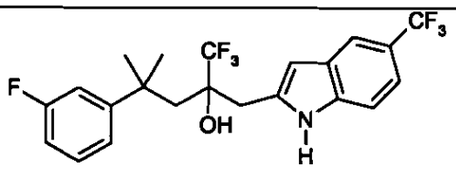
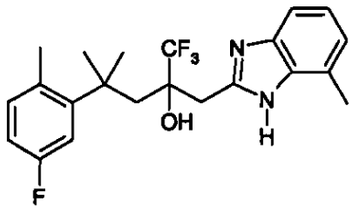
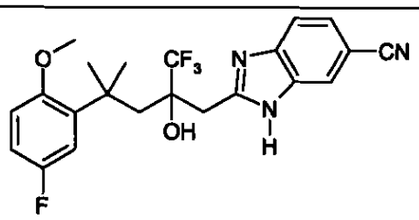
4-(5-Bromo-2,3-dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol	
4-(3-Etil-2-metoxifenil)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol	
3-[1-(2,5-Difluorofenil)ciclopropil]-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)propan-2-ol	
1,1,1-Trifluoro-3-[1-(4-fluorofenil)ciclopropil]-2-(1*H*-indol-2-ilmetil)propan-2-ol	
2-Etil-6-(4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-(6-fluoro-4-metil-1*H*-indol-2-ilmetil)-4-metilpentan-2-ol	
2-(4,6-Dimetil-1*H*-indol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol	

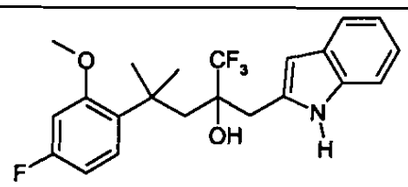
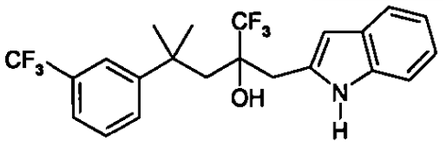
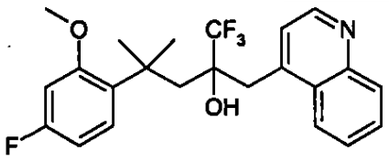
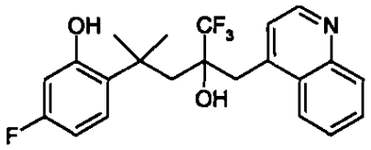
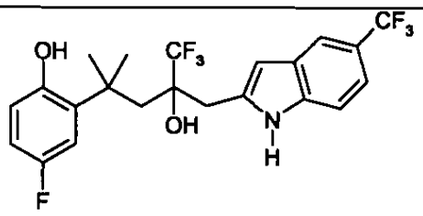
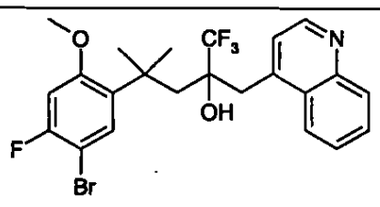
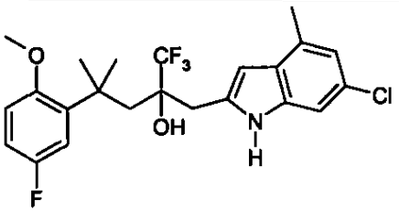
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4-(3-Etil-2-metoxifenil)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol	
2-Etil-6-[4,4,4-trifluoro-3-hidroxi-3-(1*H*-indol-2-ilmetil)-1,1-dimetilbutil]fenol	
2-[3-(6,7-Difluoro-1*H*-benzoimidazol-2-ilmetil)-4,4,4-trifluoro-3-hidroxi-1,1-dimetilbutil]-4-fluorofenol	
2-(7-Cloro-5-trifluorometil-1*H*-benzoimidazol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol	
2-(5,7-Dimetil-1*H*-benzoimidazol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol	
1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-(5-fluoro-2-metilfenil)-4-metilpentan-2-ol	
1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-(4-fluorofenil)-4-metilpentan-2-ol	

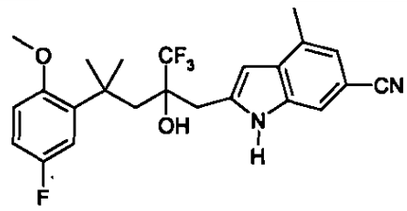
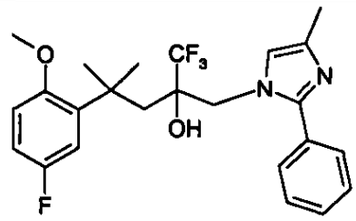
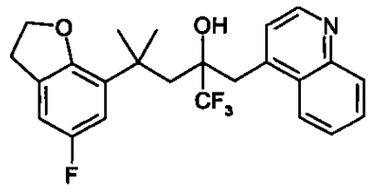
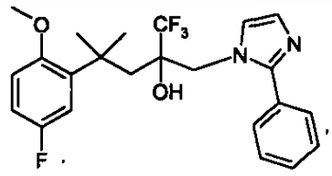
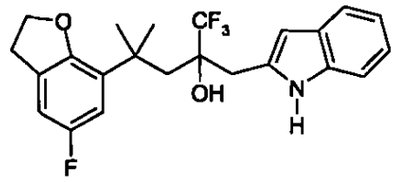
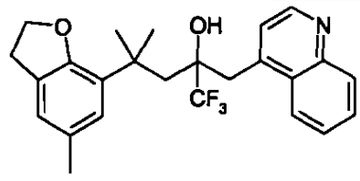
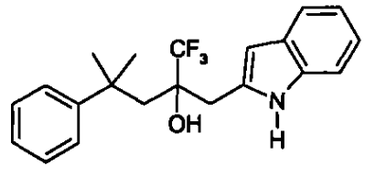
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1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-(3-fluorofenil)-4-metilpentan-2-ol	
2-[3-(5,7-Dimetil-1*H*-benzoimidazol-2-ilmetil)-4,4,4-trifluoro-3-hidroxi-1,1-dimetilbutil]-4-fluorofenol	
1,1,1-Trifluoro-4-(3-metoxifenil)-4-metil-2-quinolin-4-ilmetilpentan-2-ol	
1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-(3-metoxifenil)-4-metilpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-4-metil-2-(4-metil-1*H*-indol-2-ilmetil)pentan-2-ol	
1,1,1-Trifluoro-4-(4-fluorofenil)-4-metil-2-(4-metil-1*H*-indol-2-ilmetil)pentan-2-ol	

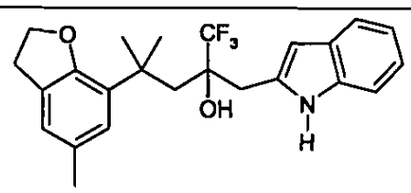
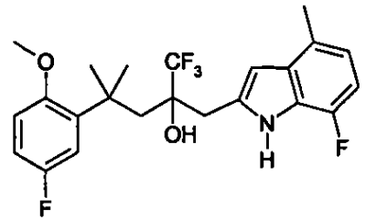
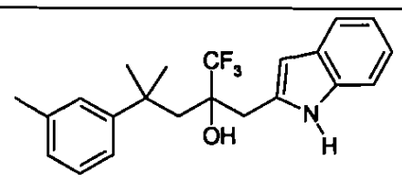
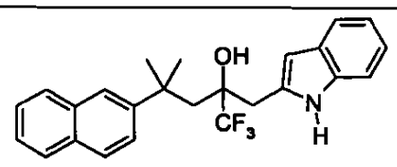
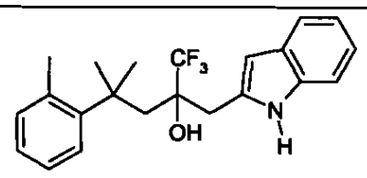
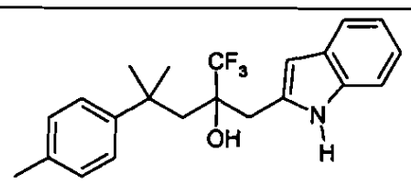
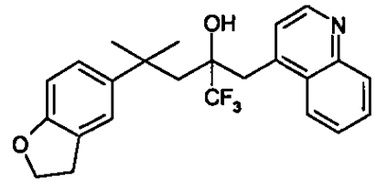
1,1,1-Trifluoro-4-(3-fluorofenil)-4-metil-2-(4-metil-1*H*-indol-2-ilmetil)pentan-2-ol	
1,1,1-Trifluoro-4-metil-2-quinolin-4-ilmetil-4-(3-trifluorometilfenil)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-4-metil-2-(5-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol	
1,1,1-Trifluoro-4-(4-fluorofenil)-4-metil-2-(5-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol	
1,1,1-Trifluoro-4-(3-fluorofenil)-4-metil-2-(5-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-4-metil-2-(7-metil-1*H*-benzoimidazol-2-ilmetil)pentan-2-ol	
2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-3*H*-benzoimidazol-5-carbonitrilo	

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol	
1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-(3-trifluorometilfenil)pentan-2-ol	
1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-quinolin-4-ilmetilpentan-2-ol	
5-Fluoro-2-(4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol	
4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(5-trifluorometil-1*H*-indol-2-ilmetil)butil]fenol	
4-(5-Bromo-4-fluoro-2-metoxifenil)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol	
2-(6-Cloro-4-metil-1*H*-indol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol	

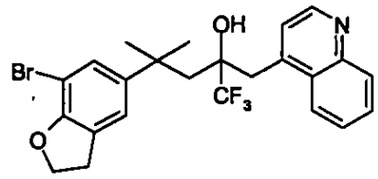
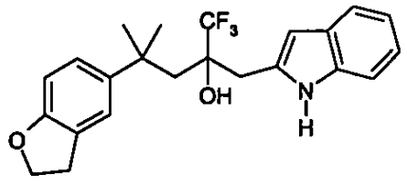
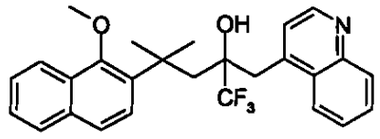
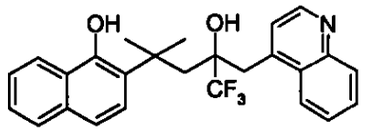
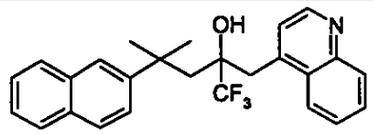
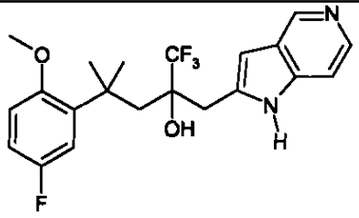
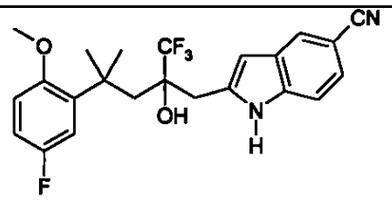
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2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo	
2-(2-Fenil-4-metilimidazol-1-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2,3-dihidrobenzofuran-7-il)-4-metil-2-quinolin-4-ilmetilpentan-2-ol	
2-(2-Fenilimidazol-1-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2,3-dihidrobenzofuran-7-il)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol	
1,1,1-Trifluoro-4-metil-4-(5-metil-2,3-dihidrobenzofuran-7-il)-2-quinolin-4-ilmetilpentan-2-ol	
1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-fenilpentan-2-ol	

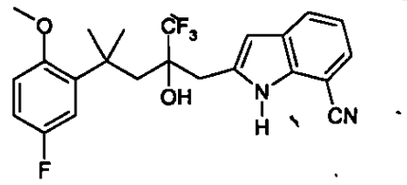
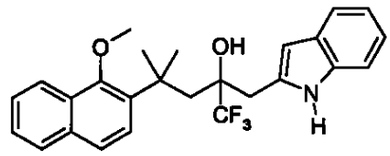
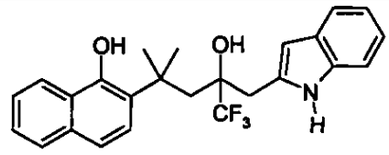
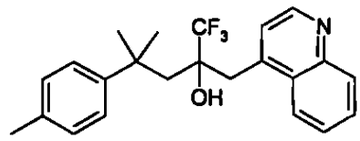
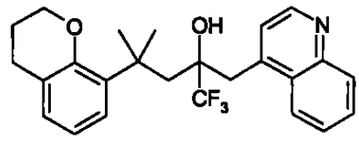
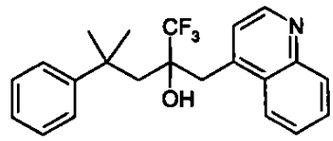
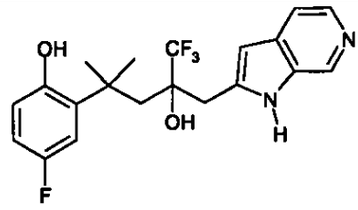
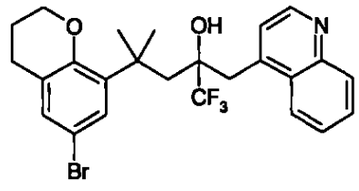
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1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-(5-metil-2,3-dihidrobenzofuran-7-il)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-(7-fluoro-4-metil-1*H*-indol-2-ilmetil)-4-metilpentan-2-ol	
1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-*m*-tolilpentan-2-ol	
1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-naftalen-2-ilpentan-2-ol	
1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-*o*-tolilpentan-2-ol	
1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-*p*-tolilpentan-2-ol	
4-(2,3-Dihidrobenzofuran-5-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol	

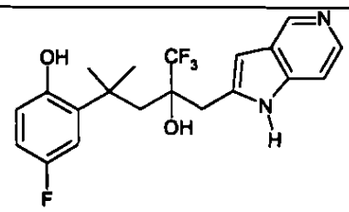
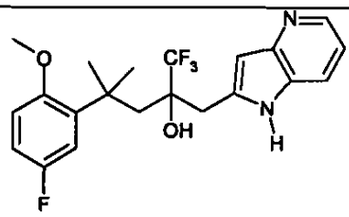
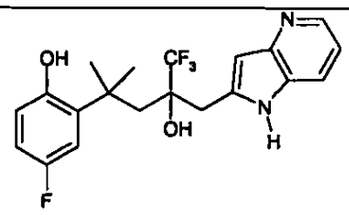
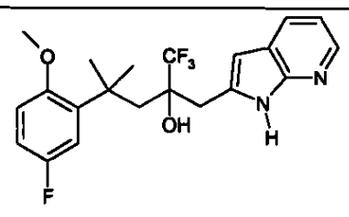
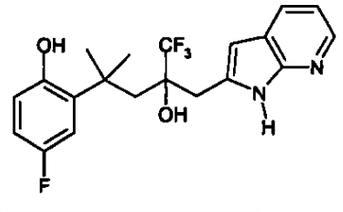
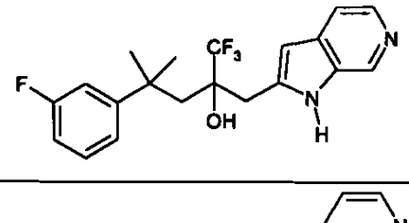
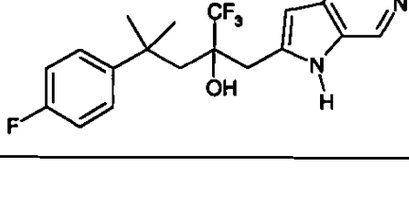
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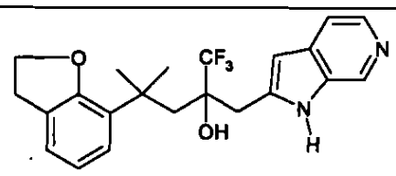
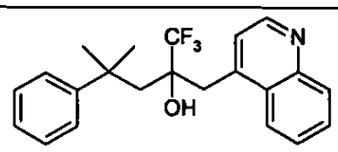
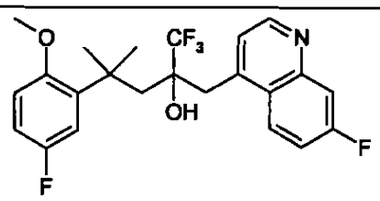
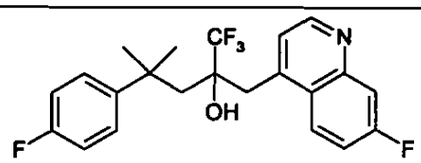
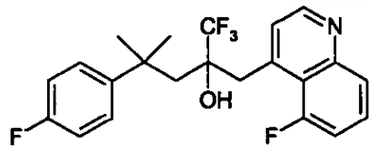
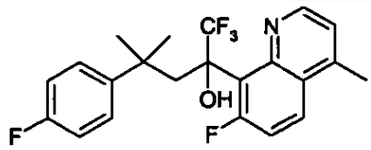
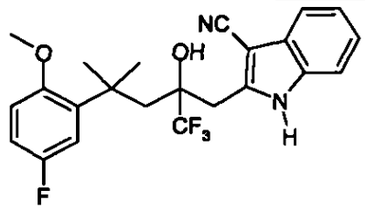
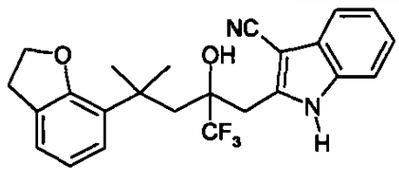
4-(7-Bromo-2,3-dihidrobenzofuran-5-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol	
4-(2,3-Dihidrobenzofuran-5-il)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol	
1,1,1-Trifluoro-4-(1-metoxinaftalen-2-il)-4-metil-2-quinolin-4-ilmetilpentan-2-ol	
2-(4,4,4-Trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)naftalen-1-ol	
1,1,1-Trifluoro-4-metil-4-naftalen-2-il-2-quinolin-4-ilmetilpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol	
2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo	

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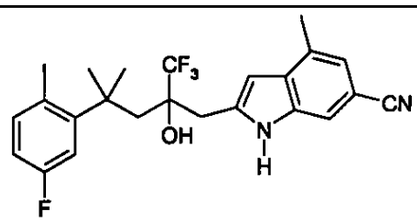
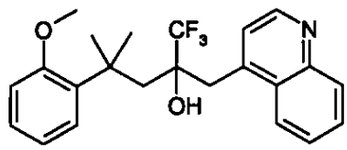
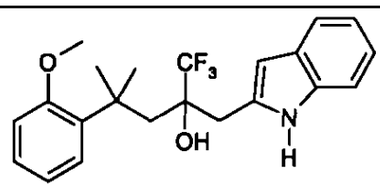
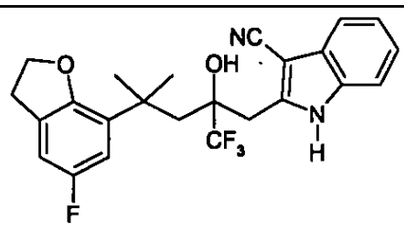
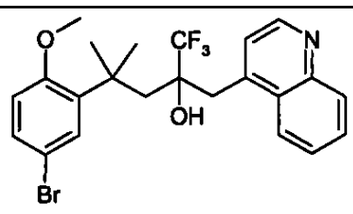
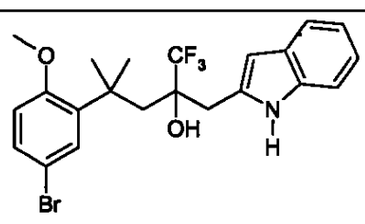
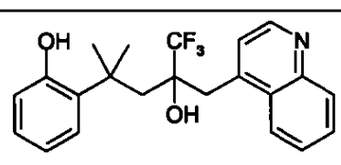
2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-7-carbonitrilo	
1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-(1-metoxinaftalen-2-il)-4-metilpentan-2-ol	
2-[4,4,4-Trifluoro-3-hidroxi-3-(1*H*-indol-2-ilmetil)-1,1-dimetilbutil]naftalen-1-ol	
1,1,1-Trifluoro-4-metil-2-quinolin-4-ilmetil-4-*p*-tolilpentan-2-ol	
4-Croman-8-il-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol	
1,1,1-Trifluoro-4-metil-4-fenil-2-quinolin-4-ilmetilpentan-2-ol	
4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)butil]fenol	
4-(6-Bromocroman-8-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol	

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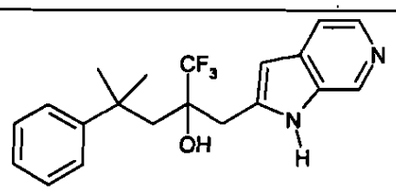
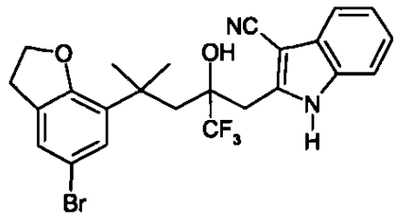
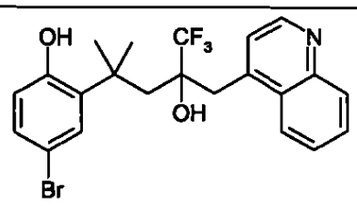
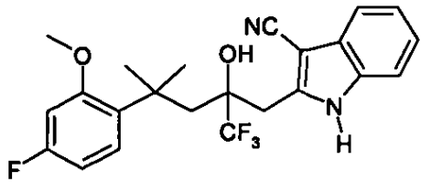
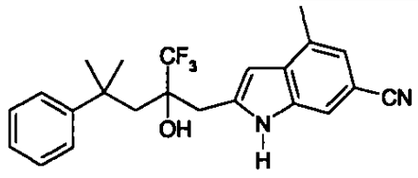
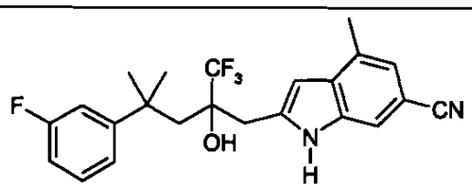
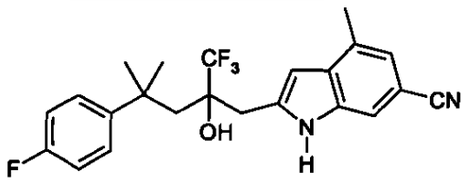
4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)butil]fenol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[3,2-*b*]piridin-2-ilmetil)pentan-2-ol	
4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[3,2-*b*]piridin-2-ilmetil)butil]fenol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[2,3-*b*]piridin-2-ilmetil)pentan-2-ol	
4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[2,3-*b*]piridin-2-ilmetil)butil]fenol	
1,1,1-Trifluoro-4-(3-fluorofenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol	
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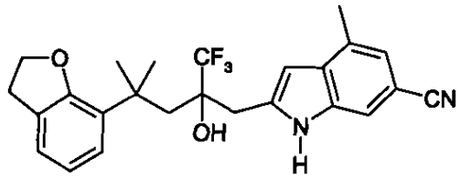
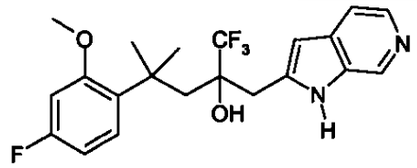
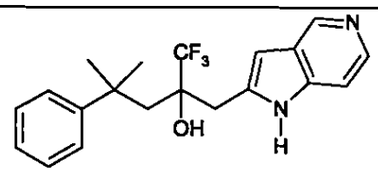
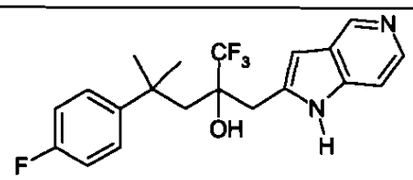
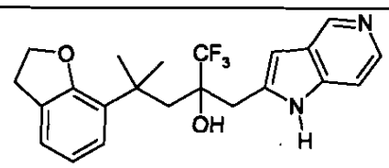
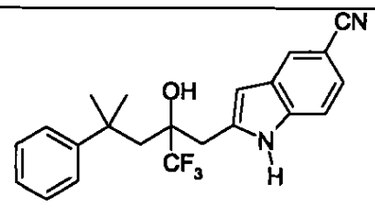
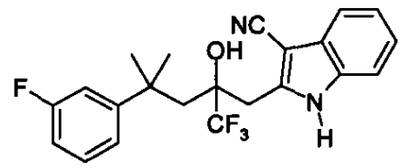
4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol	
1,1,1-Trifluoro-4-metil-4-fenil-2-quinolin-4-ilmetilpentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-(7-fluoroquinolin-4-ilmetil)-4-metilpentan-2-ol	
1,1,1-Trifluoro-4-(4-fluorofenil)-2-(7-fluoroquinolin-4-ilmetil)-4-metilpentan-2-ol	
1,1,1-Trifluoro-4-(4-fluorofenil)-2-(5-fluoroquinolin-4-ilmetil)-4-metilpentan-2-ol	
1,1,1-Trifluoro-2-(7-fluoro-4-metilquinolin-8-il)-4-(4-fluorofenil)-4-metilpentan-2-ol	
2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo	
2-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo	

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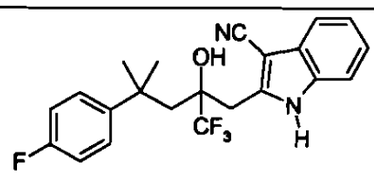
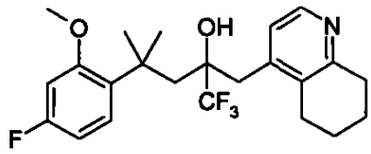
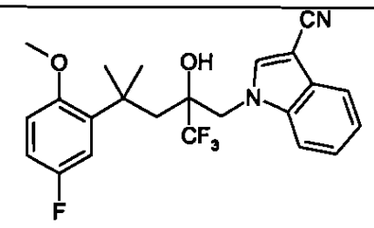
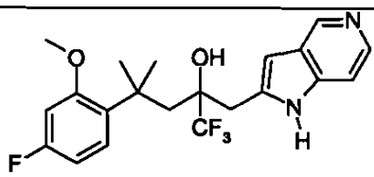
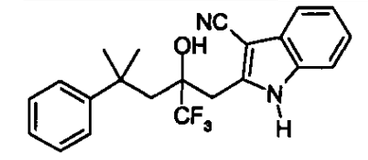
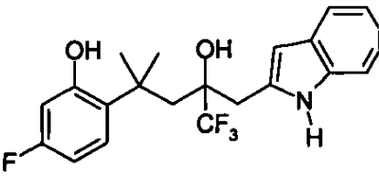
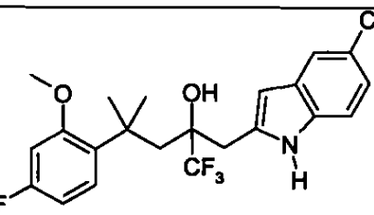
2-[4-(5-Fluoro-2-metilfenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo	
1,1,1-Trifluoro-4-(2-metoxifenil)-4-metil-2-quinolin-4-ilmetilpentan-2-ol	
1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-(2-metoxifenil)-4-metilpentan-2-ol	
2-[4-(5-Fluoro-2,3-dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo	
4-(5-Bromo-2-metoxifenil)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol	
4-(5-Bromo-2-metoxifenil)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol	
2-(4,4,4-Trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol	

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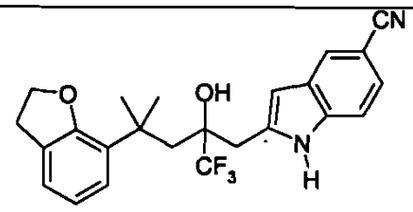
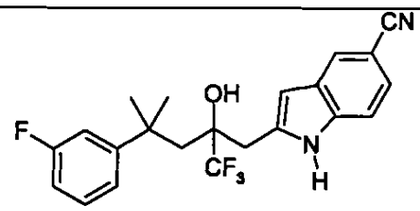
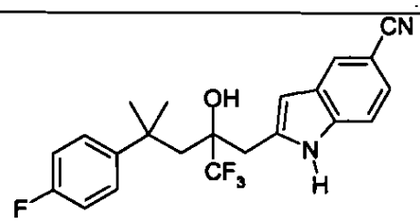
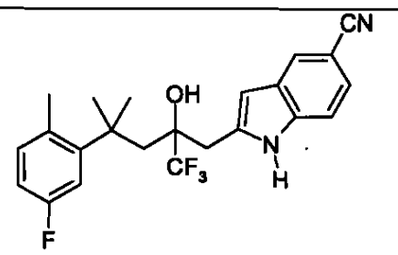
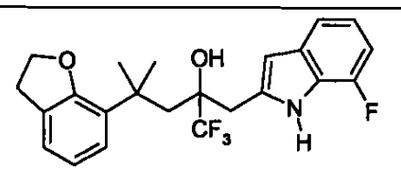
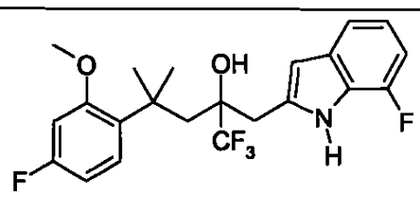
1,1,1-Trifluoro-4-metil-4-fenil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol	
2-[4-(5-Bromo-2,3-dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo	
4-Bromo-2-(4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol	
2-[4-(4-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo	
2-(2-Hidroxi-4-metil-4-fenil-2-trifluorometilpentil)-4-metil-1*H*-indol-6-carbonitrilo	
2-[4-(3-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo	
2-[4-(4-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo	

2-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo	
1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol	
1,1,1-Trifluoro-4-metil-4-fenil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol	
1,1,1-Trifluoro-4-(4-fluorofenil)-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol	
4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol	
2-(2-Hidroxi-4-metil-4-fenil-2-trifluorometilpentil)-1*H*-indol-5-carbonitrilo	
2-[4-(3-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo	

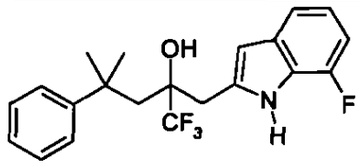
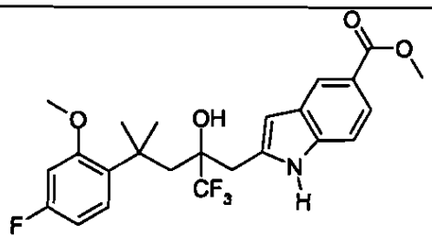
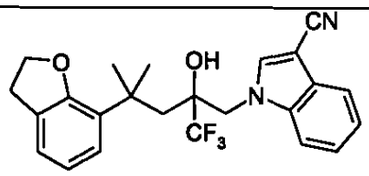
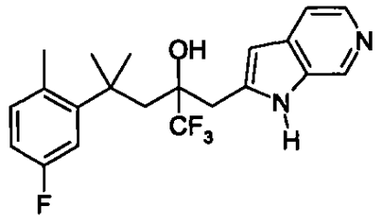
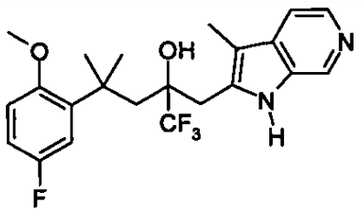
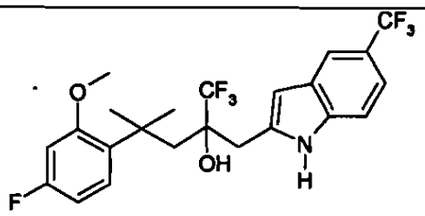
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2-[4-(4-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo	
1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-(5,6,7,8-tetrahidroquinolin-4-ilmetil)pentan-2-ol	
1-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo	
1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol	
2-(2-Hidroxi-4-metil-4-fenil-2-trifluorometilpentil)-1*H*-indol-3-carbonitrilo	
5-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)butil]fenol	
2-[4-(4-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo	

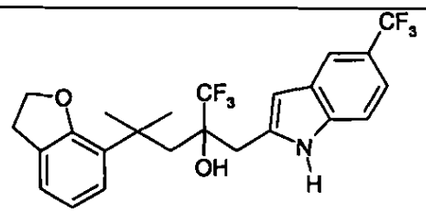
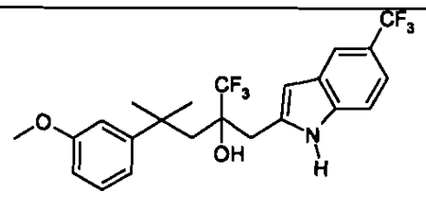
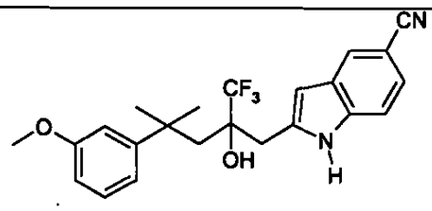
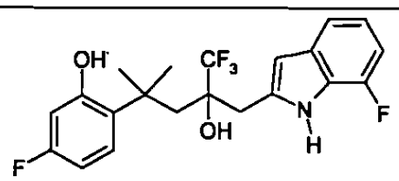
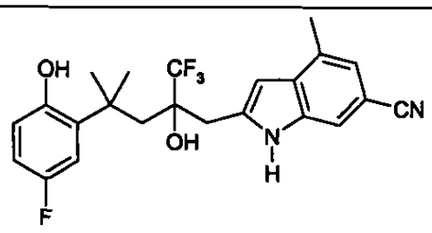
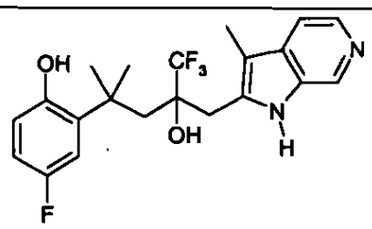
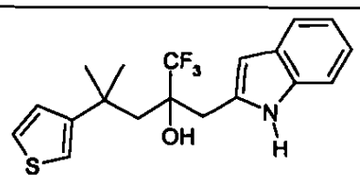
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2-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo	
2-[4-(3-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo	
2-[4-(4-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo	
2-[4-(5-Fluoro-2-metilfenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo	
4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)4-metilpentan-2-ol	
1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-(4-fluoro-2-metoxifenil)-4-metilpentan-2-ol	

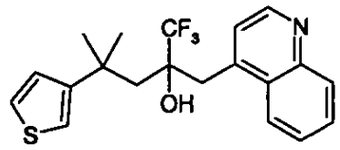
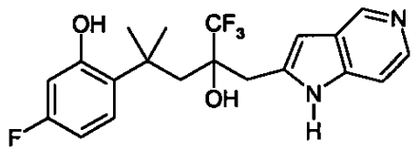
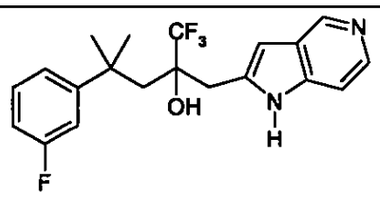
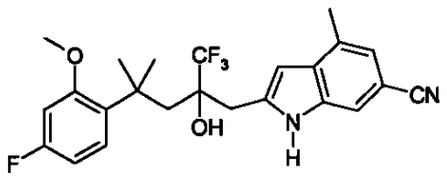
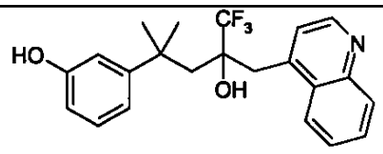
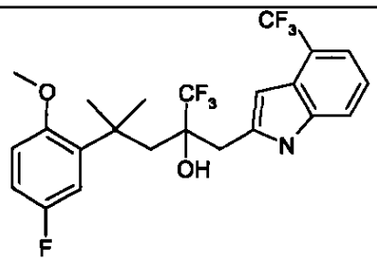
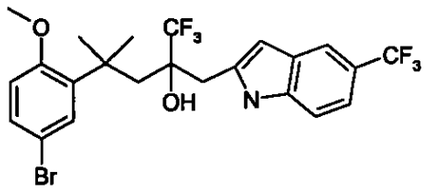
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1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-metil-4-fenilpentan-2-ol	
Éster metílico del ácido 2-[4-(4-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carboxílico	
1-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo	
1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(3-metil-1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol	
1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-(5-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol	

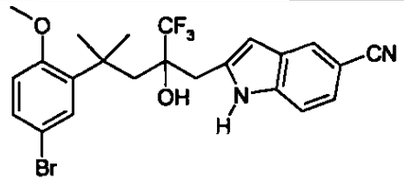
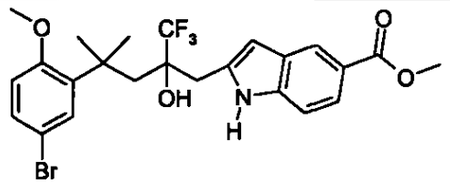
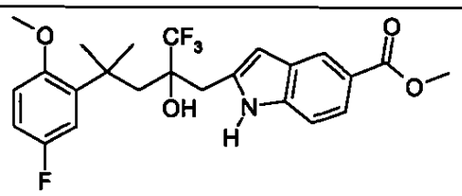
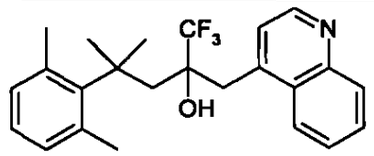
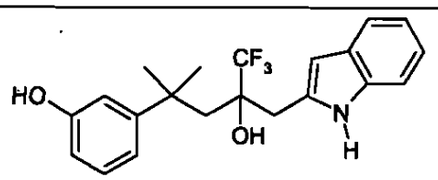
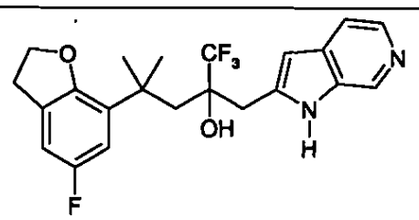
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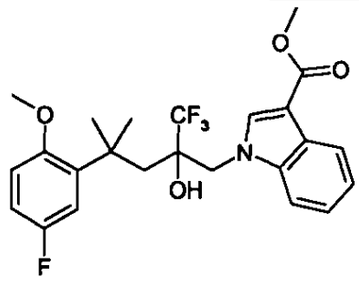
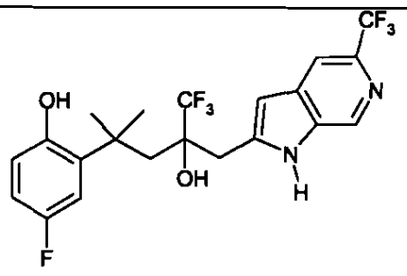
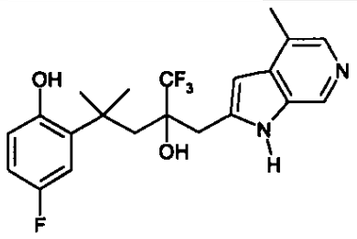
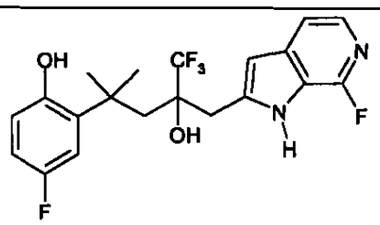
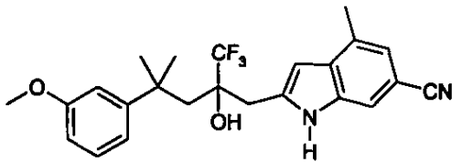
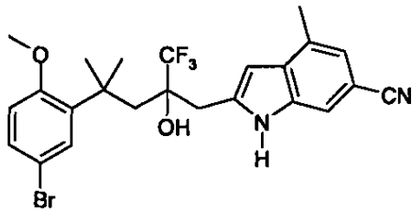
4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-(5-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol	
1,1,1-Trifluoro-4-(3-metoxifenil)-4-metil-2-(5-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol	
2-[2-Hidroxi-4-(3-metoxifenil)-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo	
5-Fluoro-2-[4,4,4-trifluoro-3-(7-fluoro-1*H*-indol-2-ilmetil)-3-hidroxi-1,1-dimetilbutil]fenol	
2-[4-(5-Fluoro-2-hidroxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo	
4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(3-metil-1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)butil]fenol	
1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-tiofen-3-ilpentan-2-ol	

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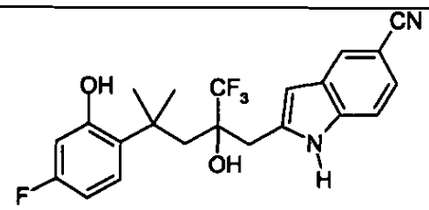
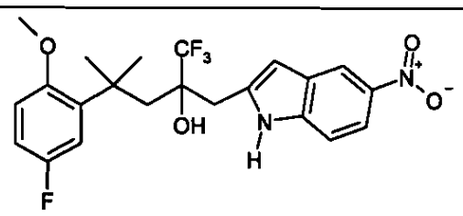
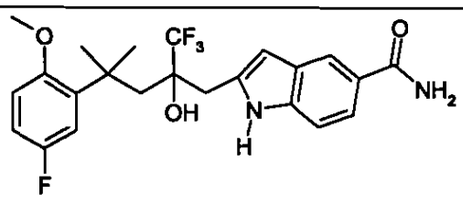
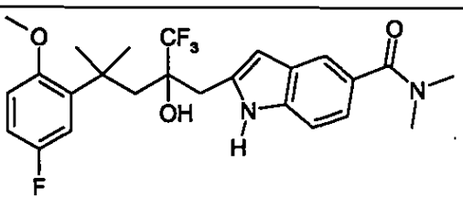
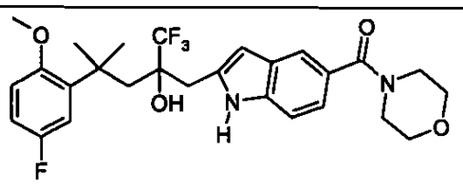
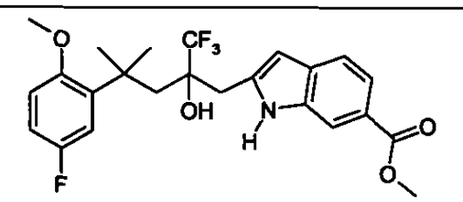
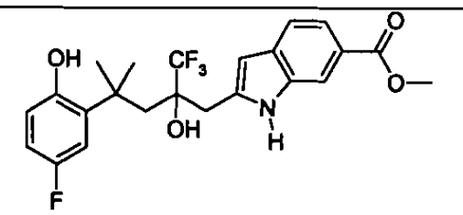
1,1,1-Trifluoro-4-metil-2-quinolin-4-ilmetil-4-tiofen-3-ilpentan-2-ol	
5-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)butil]fenol	
1,1,1-Trifluoro-4-(3-fluorofenil)-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol	
2-[4-(4-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo	
3-(4,4,4-Trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(4-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol	
4-(5-Bromo-2-metoxifenil)-1,1,1-trifluoro-4-metil-2-(5-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol	

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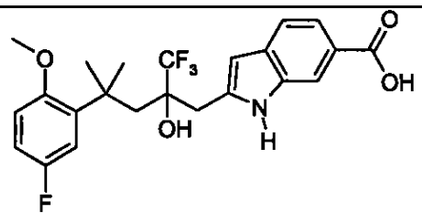
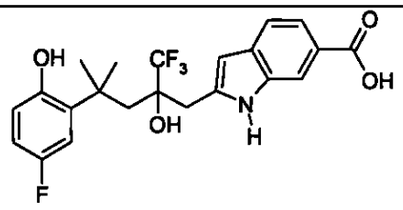
2-[4-(5-Bromo-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo	
Éster metílico del ácido 2-[4-(5-bromo-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carboxílico	
Éster metílico del ácido 2-[4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carboxílico	
4-(2,6-Dimetilfenil)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol	
3-[4,4,4-Trifluoro-3-hidroxi-3-(1*H*-indol-2-ilmetil)-1,1-dimetilbutil]fenol	
1,1,1-Trifluoro-4-(5-fluoro-2,3-dihidrobenzofuran-7-il)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol	

Éster metílico del ácido 1-[4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carboxílico	
4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[2,3-*c*]-[2-trifluorometilpiridin]-2-ilmetil)butil]fenol	
4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[2,3-*c*]-[3-metilpiridin]-2-ilmetil)butil]fenol	
4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[2,3-*c*]-[2-fluoropiridin]-2-ilmetil)butil]fenol	
2-[2-Hidroxi-4-(3-metoxifenil)-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo	
2-[4-(5-Bromo-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo	

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2-[4-(4-Fluoro-2-hidroxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo	
1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(5-nitro-1*H*-indol-2-ilmetil)pentan-2-ol	
Amida del ácido 2-[4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carboxílico	
Dimetilamida del ácido 2-[4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carboxílico	
{2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-il}morfolin-4-ilmetanona	
Éster metílico del ácido 2-[4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-6-carboxílico	
Éster metílico del ácido 2-[4-(5-fluoro-2-hidroxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-6-carboxílico	

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Ácido 2-[4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-6-carboxílico	
Ácido 2-[4-(5-fluoro-2-hidroxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-6-carboxílico	
o uno de sus tautómeros, profármacos, solvatos o sales.	

Compuestos preferidos de Fórmula (IA) incluyen los siguientes:

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-(piridin-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(5-fenilbenzoxazol-2-ilmetil)pentan-2-ol;

2-Benzofuran-2-ilmetil-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(3-metilbenzofuran-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(3-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

6-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]nicotinonitrilo;

2-(1*H*-Indol-2-ilmetil)-1,1,1-trifluoro-4-(4-fluorofenil)-4-metilpentan-2-ol;

2-(6-Cloro-4-trifluorometilpiridin-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

2-(5-Cloro-7-fluoro-1*H*-indol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

4-(3,4-Diclorofenil)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

2-(2,6-Dicloropiridin-4-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

2-[3-(2,6-Dicloropiridin-4-ilmetil)-4,4,4-trifluoro-3-hidroxi-1,1-dimetilbutil]-4-fluorofenol;

4-Fluoro-2-(4,4,4-trifluoro-3-hidroxi-3-isoquinolin-1-ilmetil-1,1-dimetilbutil)fenol;

4-(5-Bromo-2,3-dihidrobenzofuran-7-il)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-piridin-2-ilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(6-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

2-(1*H*-Bencimidazol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(6-fluoro-1*H*-indol-2-ilmetil)-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorofenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(quinolin-4-ilmetil)pentan-2-ol;

4-(2,3-dihidro-5-cianobenzofuran-7-il)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(2-cloropiridin-4-ilmetil)pentan-2-ol;

4-(3,4-Difluorofenil)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-hidroxifenil)-4-metil-2-(2-cloropiridin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(2-cloroquinolin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-hidroxifenil)-4-metil-2-(2-cloroquinolin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-(4-metoxifenil)-4-metilpentan-2-ol;

4-[4,4,4-Trifluoro-3-hidroxi-3-(1*H*-indol-2-ilmetil)-1,1-dimetilbutil]fenol;

1,1,1-Trifluoro-2-(5-fluoro-1*H*-indol-2-ilmetil)-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(5-metil-1*H*-indol-2-ilmetil)-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

4-(2,3-dihidrobenzofuran-7-il)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

2-Bencimidazol-1-ilmetil-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-metilfenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

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1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(6-clorobencimidazol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(2-fluoropiridin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(2-bromopiridin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(7-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(4-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(5-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(7-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(7-metil-1*H*-benzoimidazol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(6-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(6-trifluorometil-1*H*-benzoimidazol-2-ilmetil)pentan-2-ol;

2-(5-Cloro-6-fluoro-1*H*-benzoimidazol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-3-[1-(5-fluoro-2-metoxifenil)ciclopropil]-2-(1*H*-indol-2-ilmetil)propan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(4-metil-1*H*-indol-2-

ilmetil)butil]fenol;

4-Fluoro-2-[4,4,4-trifluoro-3-(7-fluoro-1*H*-indol-2-ilmetil)-3-hidroxi-1,1-dimetilbutil]fenol;

1,1,1-Trifluoro-2-(6-fluoro-1*H*-benzoimidazol-2-ilmetil)-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

2-(6,7-Difluoro-1*H*-benzoimidazol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(5-Bromo-2,3-dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(3-Etil-2-metoxifenil)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-3-[1-(4-fluorofenil)ciclopropil]-2-(1*H*-indol-2-ilmetil)propan-2-ol;

2-Etil-6-(4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-(6-fluoro-4-metil-1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

2-(4,6-Dimetil-1*H*-indol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

4-(3-Etil-2-metoxifenil)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

2-Etil-6-[4,4,4-trifluoro-3-hidroxi-3-(1*H*-indol-2-ilmetil)-1,1-dimetilbutil]fenol;

2-[3-(6,7-Difluoro-1*H*-benzoimidazol-2-ilmetil)-4,4,4-trifluoro-3-hidroxi-1,1-dimetilbutil]-4-fluorofenol;

2-(7-Cloro-5-trifluorometil-1*H*-benzoimidazol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

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2-(5,7-Dimetil-1*H*-benzoimidazol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-(5-fluoro-2-metilfenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-(4-fluorofenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-(3-fluorofenil)-4-metilpentan-2-ol;

2-[3-(5,7-Dimetil-1*H*-benzoimidazol-2-ilmetil)-4,4,4-trifluoro-3-hidroxi-1,1-dimetilbutil]-4-fluorofenol;

1,1,1-Trifluoro-4-(3-metoxifenil)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-(3-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-4-metil-2-(4-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorofenil)-4-metil-2-(4-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorofenil)-4-metil-2-(4-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-metil-2-quinolin-4-ilmetil-4-(3-trifluorometilfenil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-4-metil-2-(5-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorofenil)-4-metil-2-(5-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorofenil)-4-metil-2-(5-trifluorometil-1*H*-indol-2-ilmetil)pentan-

2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-4-metil-2-(7-metil-1*H*-benzoimidazol-2-ilmetil)pentan-2-ol;

2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-3*H*-benzoimidazol-5-carbonitrilo;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-(3-trifluorometilfenil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

5-Fluoro-2-(4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(5-trifluorometil-1*H*-indol-2-ilmetil)butil]fenol;

4-(5-Bromo-4-fluoro-2-metoxifenil)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

2-(6-Cloro-4-metil-1*H*-indol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

2-(2-Fenil-4-metilimidazol-1-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihidrobenzofuran-7-il)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

2-(2-Fenilimidazol-1-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihidrobenzofuran-7-il)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-metil-4-(5-metil-2,3-dihidrobenzofuran-7-il)-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-fenilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-(5-metil-2,3-dihidrobenzofuran-7-il)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-(7-fluoro-4-metil-1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-*m*-tolilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-naftalen-2-ilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-*o*-tolilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-*p*-tolilpentan-2-ol;

4-(2,3-Dihidrobenzofuran-5-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(7-Bromo-2,3-dihidrobenzofuran-5-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(2,3-Dihidrobenzofuran-5-il)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(1-metoxinaftalen-2-il)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

2-(4,4,4-Trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)naftalen-1-ol;

1,1,1-Trifluoro-4-metil-4-naftalen-2-il-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-

ilmetil)pentan-2-ol;

2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-7-carbonitrilo;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-(1-metoxinaftalen-2-il)-4-metilpentan-2-ol;

2-[4,4,4-Trifluoro-3-hidroxi-3-(1*H*-indol-2-ilmetil)-1,1-dimetilbutil]naftalen-1-ol;

1,1,1-Trifluoro-4-metil-2-quinolin-4-ilmetil-4-*p*-tolilpentan-2-ol;

4-Croman-8-il-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-4-metil-4-fenil-2-quinolin-4-ilmetilpentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)butil]fenol;

4-(6-Bromocroman-8-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)butil]fenol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[3,2-*b*]piridin-2-ilmetil)pentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[3,2-*b*]piridin-2-ilmetil)butil]fenol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[2,3-*b*]piridin-2-ilmetil)pentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[2,3-*b*]piridin-2-ilmetil)butil]fenol;

1,1,1-Trifluoro-4-(3-fluorofenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorofenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-metil-4-fenil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-(7-fluoroquinolin-4-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorofenil)-2-(7-fluoroquinolin-4-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorofenil)-2-(5-fluoroquinolin-4-ilmetil)-4-metilpentan-2-ol;

2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

2-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

2-[4-(5-Fluoro-2-metilfenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

1,1,1-Trifluoro-4-(2-metoxifenil)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-(2-metoxifenil)-4-metilpentan-2-ol;

2-[4-(5-Fluoro-2,3-dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

4-(5-Bromo-2-metoxifenil)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(5-Bromo-2-metoxifenil)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

2-(4,4,4-Trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

1,1,1-Trifluoro-4-metil-4-fenil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

2-[4-(5-Bromo-2,3-dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

4-Bromo-2-(4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

2-[4-(4-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometil-pentil]-1*H*-indol-3-carbonitrilo;

2-(2-Hidroxi-4-metil-4-fenil-2-trifluorometilpentil)-4-metil-1*H*-indol-6-carbonitrilo;

2-[4-(3-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

2-[4-(4-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

2-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-metil-4-fenil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorofenil)-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

2-(2-Hidroxi-4-metil-4-fenil-2-trifluorometilpentil)-1*H*-indol-5-carbonitrilo;

2-[4-(3-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

2-[4-(4-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-(5,6,7,8-tetrahidroquinolin-4-ilmetil)pentan-2-ol;

1-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

2-(2-Hidroxi-4-metil-4-fenil-2-trifluorometilpentil)-1*H*-indol-3-carbonitrilo;

5-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)butil]fenol;

2-[4-(4-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

2-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

2-[4-(3-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

2-[4-(4-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

2-[4-(5-Fluoro-2-metilfenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-(4-fluoro-2-metoxifenil)-4-

metilpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-metil-4-fenilpentan-2-ol;

Éster metílico del ácido 2-[4-(4-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carboxílico;

1-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(3-metil-1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-(5-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol;

4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-(5-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(3-metoxifenil)-4-metil-2-(5-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol;

2-[2-Hidroxi-4-(3-metoxifenil)-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

5-Fluoro-2-[4,4,4-trifluoro-3-(7-fluoro-1*H*-indol-2-ilmetil)-3-hidroxi-1,1-dimetilbutil]fenol;

2-[4-(5-Fluoro-2-hidroxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(3-metil-1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)butil]fenol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-tiofen-3-ilpentan-2-ol;

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1,1,1-Trifluoro-4-metil-2-quinolin-4-ilmetil-4-tiofen-3-ilpentan-2-ol;

5-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)butil]fenol;

1,1,1-Trifluoro-4-(3-fluorofenil)-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

2-[4-(4-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

3-(4,4,4-Trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(4-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol;

4-(5-Bromo-2-metoxifenil)-1,1,1-trifluoro-4-metil-2-(5-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol;

2-[4-(5-Bromo-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

Éster metílico del ácido 2-[4-(5-bromo-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carboxílico;

Éster metílico del ácido 2-[4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carboxílico;

4-(2,6-Dimetilfenil)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

3-[4,4,4-Trifluoro-3-hidroxi-3-(1*H*-indol-2-ilmetil)-1,1-dimetilbutil]fenol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihidrobenzofuran-7-il)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol; y

Éster metílico del ácido 1-[4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-

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trifluorometilpentil]-1*H*-indol-3-carboxílico,

o uno de sus tautómeros, profármacos, solvatos o sales.

Compuestos más preferidos de Fórmula (IA) incluyen los siguientes:

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

2-(2,6-Dicloropiridin-4-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

2-[3-(2,6-Dicloropiridin-4-ilmetil)-4,4,4-trifluoro-3-hidroxi-1,1-dimetilbutil]-4-fluorofenol;

4-(5-Bromo-2,3-dihidrobenzofuran-7-il)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

2-(1*H*-Bencimidazol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorofenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(quinolin-4-ilmetil)pentan-2-ol;

4-(2,3-dihidro-5-cianobenzofuran-7-il)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(2-cloropiridin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-hidroxifenil)-4-metil-2-(2-cloropiridin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(2-cloroquinolin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-hidroxifenil)-4-metil-2-(2-cloroquinolin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-(4-metoxifenil)-4-metilpentan-2-ol;

4-[4,4,4-Trifluoro-3-hidroxi-3-(1*H*-indol-2-ilmetil)-1,1-dimetilbutil]fenol;

1,1,1-Trifluoro-2-(5-fluoro-1*H*-indol-2-ilmetil)-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

4-(2,3-dihidrobenzofuran-7-il)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(2-bromopiridin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(7-metil-1*H*-benzoimidazol-2-ilmetil)pentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(4-metil-1*H*-indol-2-ilmetil)butil]fenol;

4-Fluoro-2-[4,4,4-trifluoro-3-(7-fluoro-1*H*-indol-2-ilmetil)-3-hidroxi-1,1-dimetilbutil]fenol;

1,1,1-Trifluoro-2-(6-fluoro-1*H*-benzoimidazol-2-ilmetil)-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

2-(6,7-Difluoro-1*H*-benzoimidazol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(5-Bromo-2,3-dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(3-Etil-2-metoxifenil)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

2-Etil-6-(4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

2-Etil-6-[4,4,4-trifluoro-3-hidroxi-3-(1*H*-indol-2-ilmetil)-1,1-dimetilbutil]fenol;

2-(5,7-Dimetil-1*H*-benzoimidazol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

2-[3-(5,7-Dimetil-1*H*-benzoimidazol-2-ilmetil)-4,4,4-trifluoro-3-hidroxi-1,1-dimetilbutil]-4-fluorofenol;

1,1,1-Trifluoro-4-(3-metoxifenil)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-(3-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-4-metil-2-(4-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorofenil)-4-metil-2-(4-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorofenil)-4-metil-2-(4-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-metil-2-quinolin-4-ilmetil-4-(3-trifluorometilfenil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-4-metil-2-(7-metil-1*H*-benzoimidazol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-(3-trifluorometilfenil)pentan-2-ol;

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1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

5-Fluoro-2-(4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

4-(5-Bromo-4-fluoro-2-metoxifenil)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

2-(2-Fenil-4-metilimidazol-1-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihidrobenzofuran-7-il)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

2-(2-Fenilimidazol-1-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihidrobenzofuran-7-il)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-metil-4-(5-metil-2,3-dihidrobenzofuran-7-il)-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-fenilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-(5-metil-2,3-dihidrobenzofuran-7-il)pentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-*m*-tolilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-naftalen-2-ilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-*o*-tolilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-*p*-tolilpentan-2-ol;

4-(2,3-Dihidrobenzofuran-5-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(7-Bromo-2,3-dihidrobenzofuran-5-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(2,3-Dihidrobenzofuran-5-il)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(1-metoxinaftalen-2-il)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

2-(4,4,4-Trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)naftalen-1-ol;

1,1,1-Trifluoro-4-metil-4-naftalen-2-il-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-(1-metoxinaftalen-2-il)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-metil-2-quinolin-4-ilmetil-4-*p*-tolilpentan-2-ol;

4-Croman-8-il-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-4-metil-4-fenil-2-quinolin-4-ilmetilpentan-2-ol;

4-(6-Bromocroman-8-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[3,2-*b*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[2,3-*b*]piridin-2-ilmetil)pentan-2-ol;

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1,1,1-Trifluoro-4-(3-fluorofenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-metil-4-fenil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-(7-fluoroquinolin-4-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorofenil)-2-(7-fluoroquinolin-4-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorofenil)-2-(5-fluoroquinolin-4-ilmetil)-4-metilpentan-2-ol;

2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

2-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

2-[4-(5-Fluoro-2-metilfenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

1,1,1-Trifluoro-4-(2-metoxifenil)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-(2-metoxifenil)-4-metilpentan-2-ol;

2-[4-(5-Fluoro-2,3-dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

4-(5-Bromo-2-metoxifenil)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(5-Bromo-2-metoxifenil)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

2-(4,4,4-Trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

1,1,1-Trifluoro-4-metil-4-fenil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

2-[4-(5-Bromo-2,3-dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

4-Bromo-2-(4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

1,1,1-Trifluoro-4-(4-fluorofenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

2-[4-(4-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometil-pentil]-1*H*-indol-3-carbonitrilo;

2-(2-Hidroxi-4-metil-4-fenil-2-trifluorometilpentil)-4-metil-1*H*-indol-6-carbonitrilo;

2-[4-(3-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

2-[4-(4-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

2-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-metil-4-fenil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

2-(2-Hidroxi-4-metil-4-fenil-2-trifluorometilpentil)-1*H*-indol-5-carbonitrilo;

2-[4-(3-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

2-[4-(4-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-(5,6,7,8-tetrahidroquinolin-4-ilmetil)pentan-2-ol;

1-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

2-(2-Hidroxi-4-metil-4-fenil-2-trifluorometilpentil)-1*H*-indol-3-carbonitrilo;

5-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)butil]fenol;

2-[4-(4-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

2-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

2-[4-(3-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

2-[4-(4-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

2-[4-(5-Fluoro-2-metilfenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)butil]fenol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-metil-4-fenilpentan-2-ol;

Éster metílico del ácido 2-[4-(4-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carboxílico;

1-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(3-metil-1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(3-metoxifenil)-4-metil-2-(5-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol;

2-[2-Hidroxi-4-(3-metoxifenil)-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)butil]fenol;

5-Fluoro-2-[4,4,4-trifluoro-3-(7-fluoro-1*H*-indol-2-ilmetil)-3-hidroxi-1,1-dimetilbutil]fenol;

2-[4-(5-Fluoro-2-hidroxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(3-metil-1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)butil]fenol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-tiofen-3-ilpentan-2-ol;

1,1,1-Trifluoro-4-metil-2-quinolin-4-ilmetil-4-tiofen-3-ilpentan-2-ol;

5-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)butil]fenol;

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1,1,1-Trifluoro-4-(3-fluorofenil)-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

3-(4,4,4-Trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

Éster metílico del ácido 2-[4-(5-bromo-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carboxílico;

Éster metílico del ácido 2-[4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carboxílico;

4-(2,6-Dimetilfenil)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

3-[4,4,4-Trifluoro-3-hidroxi-3-(1*H*-indol-2-ilmetil)-1,1-dimetilbutil]fenol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihidrobenzofuran-7-il)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

2-[2-Hidroxi-4-(3-metoxifenil)-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

2-[4-(5-Bromo-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

2-[4-(4-Fluoro-2-hidroxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(5-nitro-1*H*-indol-2-ilmetil)pentan-2-ol;

Amida del ácido 2-[4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carboxílico;

Dimetilamida del ácido 2-[4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carboxílico;

{2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-

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il}morfolin-4-ilmetanona;

Éster metílico del ácido 2-[4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-6-carboxílico;

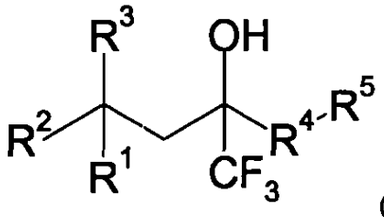
Éster metílico del ácido 2-[4-(5-fluoro-2-hidroxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-6-carboxílico;

Ácido 2-[4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-6-carboxílico; y

Ácido 2-[4-(5-fluoro-2-hidroxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-6-carboxílico,

o uno de sus tautómeros, profármacos, solvatos o sales.

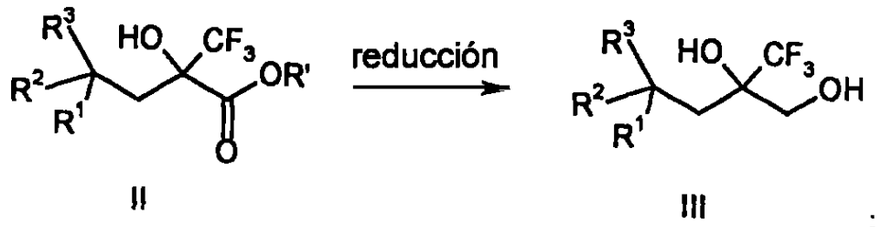
La invención también proporciona un procedimiento para preparar un compuesto de Fórmula (IA)



(IA)

en la que R^1, R^2, R^3, R^4 y R^5 son como se han definido antes, comprendiendo el procedimiento:

(a) hacer reaccionar un éster de Fórmula (II) con un agente reductor adecuado en un disolvente adecuado, formando un diol de Fórmula (III)

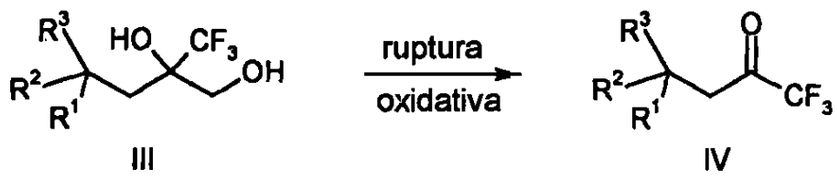


II III ;

(b) hacer reaccionar el diol de Fórmula (III) en condiciones adecuadas de ruptura

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oxidativa, formando una cetona de Fórmula (IV)



III IV

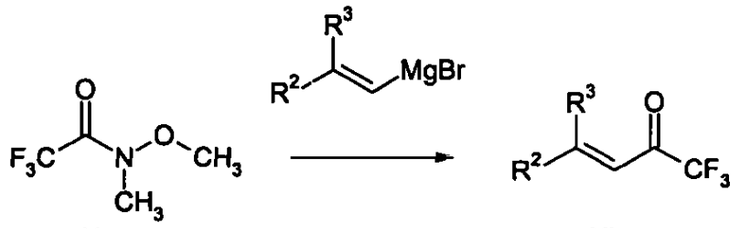
; y

(c) hacer reaccionar la cetona de Fórmula (IV) con un compuesto organometálico adecuado R^5R^4M en el que M es Li o MgX y X es Cl, Br o I, en un disolvente adecuado, formando el compuesto de Fórmula (IA)



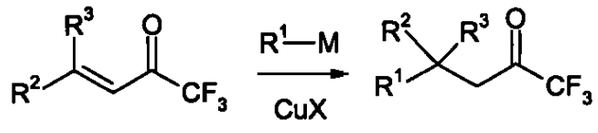
IV IA ; o

(a') hacer reaccionar la trifluoroacetamida de Fórmula (X) con un bromuro de vinil-magnesio que tenga R^2 y R^3 en un disolvente adecuado, proporcionando la trifluorometilenona de Fórmula (XI)



X XI ;

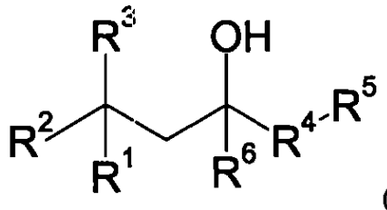
(b') hacer reaccionar la trifluorometilenona de Fórmula (XI) con un reactivo de organocobre generado a partir de un reactivo organometálico R^5R^4M en el que M es Li o MgX y una sal de cobre CuX, en la que X es Cl, Br o I, en un disolvente adecuado, formando una cetona de Fórmula (IV)



XI IV ;

y llevar a cabo la etapa (c) como se ha descrito antes.

La presente invención también se refiere a compuestos de Fórmula (IB)



(IB)

en la que:

R^1 es un grupo arilo o heteroarilo, cada uno opcionalmente sustituido independientemente con uno a tres grupos sustituyentes,

siendo cada grupo sustituyente de R^1 independientemente alquilo C_1-C_5, alquenilo C_2-C_5, alquinilo C_2-C_5, cicloalquilo C_3-C_8, heterociclilo, arilo, heteroarilo, alcoxi C_1-C_5, alqueniloxi C_2-C_5, alquiniloxi C_2-C_5 , ariloxi, acilo, (alcoxi C_1-C_5)carbonilo, alcanoiloxi C_1-C_5, alcanoilo C_1-C_5, aroilo, aminocarbonilo, (alquil C_1-C_5)aminocarbonilo, di(alquil C_1-C_5)aminocarbonilo, aminocarboniloxi, (alquil C_1-C_5)aminocarboniloxi, di(alquil C_1-C_5)aminocarboniloxi, (alcanoil C_1-C_5)amino, (alcoxi C_1-C_5)carbonilamino, (alquil C_1-C_5)sulfonilamino, aminosulfonilo, (alquil C_1-C_5)aminosulfonilo, di(alquil C_1-C_5)aminosulfonilo, halógeno, hidroxi, carboxi, ciano, trifluorometilo, trifluorometoxi, nitro o amino, estando el átomo de nitrógeno opcionalmente mono- o disustituido independientemente con alquilo C_1-C_5 o arilo; o ureido, en el que el átomo de nitrógeno está opcionalmente sustituido independientemente con alquilo C_1-C_5; o (alquil C_1-C_5)tio, en el que el átomo de azufre está opcionalmente oxidado a sulfóxido o sulfona,

estando cada grupo sustituyente de R^1 opcionalmente sustituido independientemente con uno a tres grupos sustituyentes seleccionados de metilo, metoxi, halógeno, hidroxi, oxo, ciano o amino,

R^2 y R^3 son cada uno independientemente alquilo C_1-C_5;

R^4 es alquilo C_1-C_5, alquenilo C_2-C_5 o alquinilo C_2-C_5, cada uno opcionalmente

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sustituido independientemente con uno a tres grupos sustituyentes,

siendo cada grupo sustituyente de R^4 independientemente alquilo C_1-C_3, hidroxi, halógeno u oxo;

R^5 es un grupo heteroarilo sustituido opcionalmente independientemente con uno a tres grupos sustituyentes,

siendo cada grupo sustituyente de R^5 independientemente alquilo C_1-C_5, alquenilo C_2-C_5, alquinilo C_2-C_5, cicloalquilo C_3-C_8, heterociclilo, arilo, heteroarilo, alcoxi C_1-C_5, alqueniloxi C_2-C_5, alquiniloxi C_2-C_5, ariloxi, acilo, (alcoxi C_1-C_5)carbonilo, alcanoiloxi C_1-C_5, aminocarbonilo, alquilaminocarbonilo, dialquilaminocarbonilo, aminocarboniloxi, (alquil C_1-C_5)aminocarboniloxi, di(alquil C_1-C_5)aminocarboniloxi, (alcanoil C_1-C_5)amino, (alcoxi C_1-C_5)carbonilamino, (alquil C_1-C_5)sulfonilamino, (alquil C_1-C_5)aminosulfonilo, di(alquil C_1-C_5)aminosulfonilo, halógeno, hidroxi, carboxi, ciano, trifluorometilo, trifluorometoxi, trifluorometiltio, nitro o amino, estando el átomo de nitrógeno opcionalmente mono- o disustituido independientemente con alquilo C_1-C_5; o ureido en el que el átomo de nitrógeno está opcionalmente sustituido independientemente con alquilo C_1-C_5; o alquil C_1-C_5, en el que el átomo de azufre está opcionalmente oxidado a un sulfóxido o sulfona,

estando cada grupo sustituyente de R^5 opcionalmente sustituido independientemente con uno a tres grupos sustituyentes seleccionados de alquilo C_1-C_3, alcoxi C_1-C_3, halógeno, hidroxi, oxo, ciano, amino o trifluorometilo; y

R^6 es alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, carbociclo, heterociclilo, arilo, heteroarilo, carbociclo-alquilo C_1-C_8, aril-alquilo C_1-C_8, aril-haloalquilo C_1-C_8, heterociclil-alquilo C_1-C_8, heteroaril-alquilo C_1-C_8, carbociclo-alquenilo C_2-C_8, aril-alquenilo C_2-C_8, heterociclil-alquenilo C_2-C_8 o heteroaril-alquenilo C_2-C_8, cada uno opcionalmente sustituido independientemente con uno a tres grupos sustituyentes,

siendo cada grupo sustituyente de R^6 es independientemente alquilo C_1-C_5, alquenilo C_2-C_5, alquinilo C_2-C_5, cicloalquilo C_3-C_8, fenilo, alcoxi C_1-C_5, fenoxi, alcanoilo C_1-C_5, aroilo, (alcoxi C_1-C_5)carbonilo, alcanoiloxi C_1-C_5,

aminocarboniloxi, (alquil C_1-C_5)aminocarboniloxi, di(alquil C_1-C_5)aminocarboniloxi, aminocarbonilo, (alquil C_1-C_5)aminocarbonilo, di(alquil C_1-C_5)aminocarbonilo, (alcanoil C_1-C_5)amino, (alcoxi C_1-C_5)carbonilamino, (alquil C_1-C_5)sulfonilamino, (alquil C_1-C_5)aminosulfonilo, di(alquil C_1-C_5)aminosulfonilo, halógeno, hidroxi, carboxi, ciano, oxo, trifluorometilo, nitro, amino, estando el átomo de nitrógeno opcionalmente mono- o disustituido independientemente con alquilo C_1-C_5; o ureido en el que el átomo de nitrógeno está opcionalmente sustituido independientemente con alquilo C_1-C_5; o alquiltio C_1-C_5 en el que el átomo de azufre está opcionalmente oxidado a un sulfóxido o sulfona,

no pudiendo ser R^6 trifluorometilo,

o uno de sus tautómeros, profármacos, solvatos o sales.

Otro aspecto de la invención incluye un compuesto de Fórmula (IB), en la que:

R^1 es tienilo, fenilo, naftilo, dihidrobenzofuranilo, benzofuranilo, cromanilo, dihidroindolilo, indolilo, dihidrobenzotienilo, benzotienilo, benzodioxolanilo, benzoxazolilo, bencisoxazolilo, benzopirazolilo, bencimidazolilo, quinolinilo, piridinilo, pirimidinilo o pirazinilo, cada uno opcionalmente sustituido independientemente con uno a tres grupos sustituyentes,

siendo cada grupo sustituyente de R^1 independientemente alquilo C_1-C_3, alquenilo C_2-C_3, alquinilo C_2-C_3, alcoxi C_1-C_3, alqueniloxi C_2-C_3, alcanoilo C_1-C_3, (alcoxi C_1-C_3)carbonilo, alcanoiloxi C_1-C_3, halógeno, hidroxi, carboxi, ciano, trifluorometilo, nitro o (alquil C_1-C_3)tio, en el que el átomo de azufre está opcionalmente oxidado a un sulfóxido o sulfona,

estando cada grupo sustituyente de R^1 opcionalmente sustituido independientemente con un grupo sustituyente seleccionado de metilo, metoxi, halógeno, hidroxi, oxo, ciano o amino;

R^2 y R^3 son cada uno independientemente alquilo C_1-C_3;

R^4 es CH_2;

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R^5 es un grupo imidazolilo, piridilo, indolilo, azaindolilo, diazaindolilo, benzofuranilo, furanopiridinilo, furanopirimidinilo, benzotienilo, tienopiridinilo, tienopirimidinilo, benzoxazolilo, oxazolopiridinilo, benzotiazolilo, tiazolopiridinilo, bencimidazolilo, imidazolopiridinilo, quinolinilo o isoquinolinilo, cada uno opcionalmente sustituido independientemente con uno a tres grupos sustituyentes,

siendo cada grupo sustituyente de R^5 independientemente alquilo C_1-C_3, alquenilo C_2-C_3, fenilo, alcoxi C_1-C_3, metoxicarbonilo, aminocarbonilo, (alquil C_1-C_3)aminocarbonilo, di(alquil C_1-C_3)aminocarbonilo, heterociclilcarbonilo, fluoro, cloro, bromo, ciano, trifluorometilo o (alquil C_1-C_3)tio, en el que el átomo de azufre está opcionalmente oxidado a un sulfóxido o sulfona,

estando cada grupo sustituyente de R^5 opcionalmente sustituido independientemente con un grupo sustituyente seleccionado de metilo, metoxi, fluoro, cloro, bromo o trifluorometilo; y

R^6 es alquilo C_1-C_5, alquenilo C_2-C_5, cicloalquilo C_3-C_6, fenilo, cicloalquil C_3-C_6-alquilo C_1-C_3, fenil-alquilo C_1-C_3, fenil-haloalquilo C_1-C_3, cicloalquil C_3-C_6-alquenilo C_2-C_3, fenil-alquenilo C_2-C_3, cada uno opcionalmente sustituido independientemente con uno a tres grupos sustituyentes,

siendo cada grupo sustituyente de R^6 independientemente alquilo C_1-C_3, alquenilo C_2-C_3, alquinilo C_2-C_3, alcoxi C_1-C_3, aminocarbonilo, (alquil C_1-C_3)aminocarbonilo, di(alquil C_1-C_3)aminocarbonilo, halógeno, hidroxi, carboxi, ciano, trifluorometilo, nitro o alquiltio C_1-C_3, en el que el átomo de azufre está opcionalmente oxidado a un sulfóxido o sulfona,

o uno de sus tautómeros, profármacos, solvatos o sales.

Otro aspecto más de la invención incluye compuestos de Fórmula (IB), en la que:

R^1 es tienilo, fenilo, naftilo, piridilo, cromanilo, dihidrobenzofuranilo o benzofuranilo, cada uno opcionalmente sustituido independientemente con uno o dos grupos sustituyentes,

siendo cada grupo sustituyente de R^1 independientemente metilo, etilo, metoxi,

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etoxi, fluoro, cloro, bromo, hidroxi, trifluorometilo o ciano;

R^2 y R^3 son cada uno metilo;

R^4 es CH_2;

R^5 es un grupo piridilo, indolilo, azaindolilo, benzofuranilo, furanopiridinilo, tienopiridinilo, benzoxazolilo, bencimidazolilo, quinolinilo o isoquinolinilo, cada uno opcionalmente sustituido independientemente con uno a tres grupos sustituyentes,

siendo cada grupo sustituyente de R^5 independientemente metilo, fenilo, metoxicarbonilo, aminocarbonilo, metilaminocarbonilo, dimetilaminoaminocarbonilo, morfolinilcarbonilo, fluoro, cloro, bromo, ciano, o trifluorometilo; y

R^6 es alquilo C_1-C_5, cicloalquilo C_3-C_6, cicloalquil C_3-C_6-metil- o bencilo, cada uno opcionalmente sustituido independientemente con uno a tres grupos sustituyentes,

siendo cada grupo sustituyente de R^6 independientemente metilo, metoxi, fluoro, cloro, bromo, ciano, trifluorometilo o hidroxi,

o uno de sus tautómeros, profármacos, solvatos o sales.

Otro aspecto más de la invención incluye compuestos de Fórmula (IB), en la que:

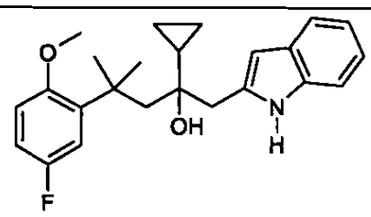
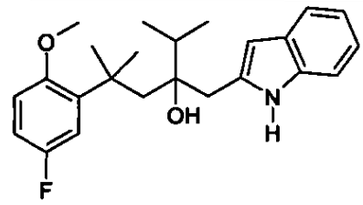
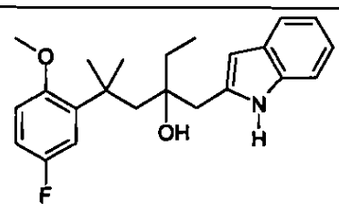
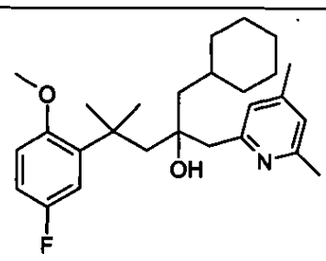
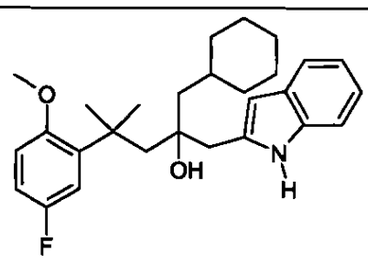
R^1 es fenilo, dihidrobenzofuranilo o benzofuranilo, cada uno opcionalmente sustituido independientemente con uno a tres grupos sustituyentes,

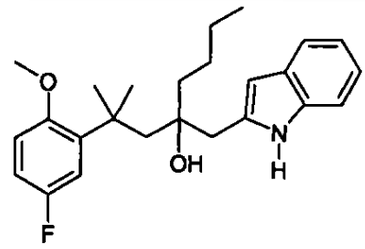
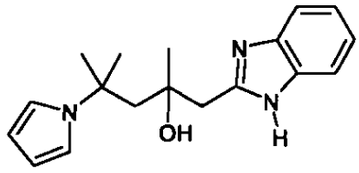
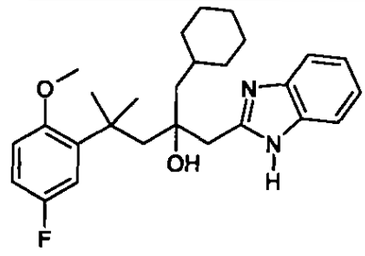
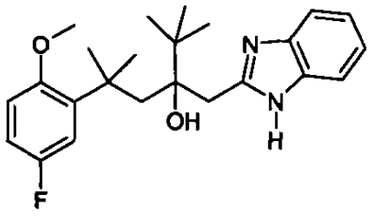
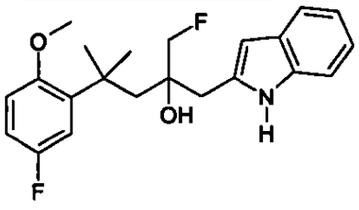
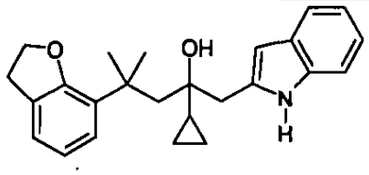
siendo cada grupo sustituyente de R^1 independientemente alquilo C_1-C_3, alquenilo C_2-C_3, alquinilo C_2-C_3, alcoxi C_1-C_3, alqueniloxi C_2-C_3, alcanoilo C_1-C_3, (alcoxi C_1-C_3)carbonilo, alcanoiloxi C_1-C_3, halógeno, hidroxi, carboxi, ciano, trifluorometilo, nitro o alquiltio C_1-C_3, en el que el átomo de azufre está opcionalmente oxidado a un sulfóxido o sulfona; y

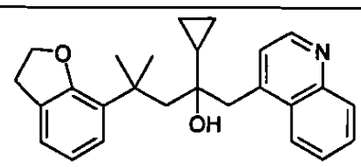
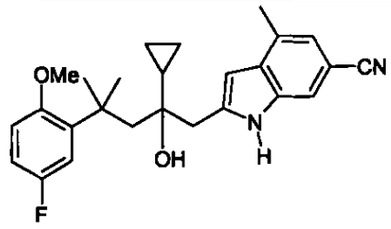
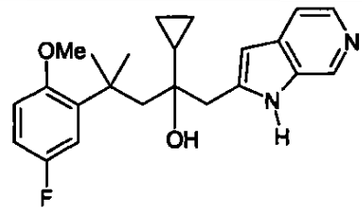
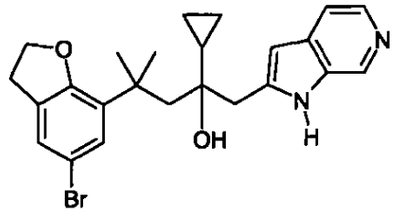
R^2 y R^3 son cada uno independientemente alquilo C_1-C_3,

o uno de sus tautómeros, profármacos, solvatos o sales.

Los siguientes compuestos son representativos de la Fórmula (IB) conforme a la invención:

Nombre del compuesto	Estructura del compuesto
2-Ciclopropil-4-(5-fluoro-2-metoxifenil)-1-(1*H*-indol-2-il)-4-metilpentan-2-ol	
5-(5-Fluoro-2-metoxifenil)-3-(1*H*-indol-2-ilmetil)-2,5-dimetilhexan-3-ol	
5-(5-Fluoro-2-metoxifenil)-3-(1*H*-indol-2-ilmetil)-5-metilhexan-3-ol	
2-Ciclohexilmetil-1-(4,6-dimetilpiridin-2-il)-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol	
2-Ciclohexilmetil-4-(5-fluoro-2-metoxifenil)-1-(1*H*-indol-2-il)-4-metilpentan-2-ol	

7-(5-Fluoro-2-metoxifenil)-5-(1*H*-indol-2-ilmetil)-7-metiloctan-5-ol	
2-(Bencimidazol-2-ilmetil)-4-metil-4-(pirrol-1-il)pentan-2-ol	
1-(1*H*-Benzoimidazol-2-il)-2-ciclohexilmetil-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol	
5-(5-Fluoro-2-metoxifenil)-3-(bencimidazol-2-ilmetil)-2,2,5-trimetilhexan-3-ol	
4-(5-Fluoro-2-metoxifenil)-2-fluorometil-1-(1*H*-indol-2-il)-4-metilpentan-2-ol	
2-Ciclopropil-4-(2,3-dihidrobenzofuran-7-il)-1-(1*H*-indol-2-il)-4-metilpentan-2-ol	

2-Ciclopropil-4-(2,3-dihidrobenzofuran-7-il)-1-(quinolin-4-il)-4-metilpentan-2-ol	
2-Ciclopropil-4-(5-fluoro-2-metoxifenil)-1-(6-ciano-4-metilindol-2-il)-4-metilpentan-2-ol	
2-Ciclopropil-4-(5-fluoro-2-metoxifenil)-4-metil-1-(1*H*-pirrolo[2,3-*c*]piridin-2-il)pentan-2-ol	
4-(5-Bromo-2,3-dihidrobenzofuran-7-il)-2-ciclopropil-4-metil-1-(1*H*-pirrolo[2,3-*c*]piridin-2-il)pentan-2-ol	
o uno de sus tautómeros, profármacos, solvatos o sales.	

Compuestos preferidos de Fórmula (IE) incluyen los siguientes:

2-Ciclopropil-4-(5-fluoro-2-metoxifenil)-1-(1*H*-indol-2-il)-4-metilpentan-2-ol;

5-(5-Fluoro-2-metoxifenil)-3-(indol-2-ilmetil)-2,5-dimetilhexan-3-ol;

5-(5-Fluoro-2-metoxifenil)-3-(indol-2-ilmetil)-5-metilhexan-3-ol;

1-Ciclohexil-4-(5-fluoro-2-metoxifenil)-2-(indol-2-ilmetil)-4-metilpentan-2-ol;

5-(5-Fluoro-2-metoxifenil)-3-(bencimidazol-2-ilmetil)-2,2,5-trimetilhexan-3-ol;

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4-(5-Fluoro-2-metoxifenil)-2-fluorometil-1-(1*H*-indol-2-il)-4-metilpentan-2-ol;

2-Ciclopropil-4-(2,3-dihidrobenzofuran-7-il)-1-(1*H*-indol-2-il)-4-metilpentan-2-ol;

2-Ciclopropil-4-(2,3-dihidrobenzofuran-7-il)-1-(quinolin-4-il)-4-metilpentan-2-ol;

2-Ciclopropil-4-(5-fluoro-2-metoxifenil)-1-(6-ciano-4-metilindol-2-il)-4-metilpentan-2-ol;

2-Ciclopropil-4-(5-fluoro-2-metoxifenil)-4-metil-1-(1*H*-pirrolo[2,3-*c*]piridin-2-il)pentan-2-ol; y

4-(5-Bromo-2,3-dihidrobenzofuran-7-il)-2-ciclopropil-4-metil-1-(1*H*-pirrolo[2,3-*c*]piridin-2-il)pentan-2-ol,

o uno de sus tautómeros, profármacos, solvatos o sales.

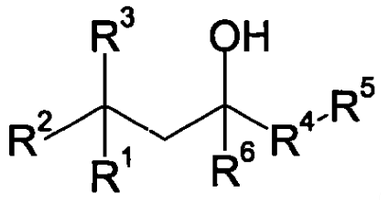
Compuestos más preferidos de Fórmula (IB) incluyen:

2-Ciclopropil-4-(2,3-dihidrobenzofuran-7-il)-1-(1*H*-indol-2-il)-4-metilpentan-2-ol; y

2-Ciclopropil-4-(5-fluoro-2-metoxifenil)-4-metil-1-(1*H*-pirrolo[2,3-*c*]piridin-2-il)pentan-2-ol;

o uno de sus tautómeros, profármacos, solvatos o sales.

La invención proporciona además procedimientos para preparar un compuesto de Fórmula (IB). Un procedimiento para preparar un compuesto Fórmula (IB)

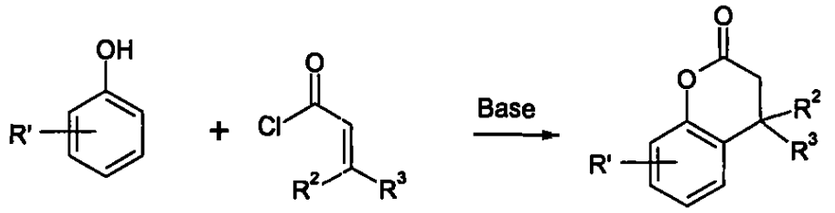


(IB)

en la que R^1 es un grupo 2-metoxifenilo opcionalmente sustituido y R^2, R^3, R^4, R^5 y R^6 son como se definen antes, comprendiendo el procedimiento:

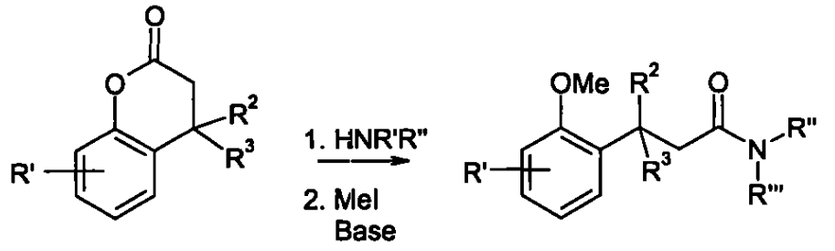
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(a) hacer reaccionar un fenol opcionalmente sustituido de Fórmula (XXII) con un cloruro de acriloilo de Fórmula (XIII) en presencia de una base adecuada, seguido por ciclación del éster intermedio por tratamiento con un ácido de Lewis adecuado, formando una lactona de Fórmula (XIV)



XII XIII XIV ;

(b) hacer reaccionar la lactona de Fórmula (XIV) con una amina adecuada HNR'R'', seguido por tratamiento del fenol intermedio con yoduro de metilo en presencia de una base adecuada formando una amida de Fórmula (XV)



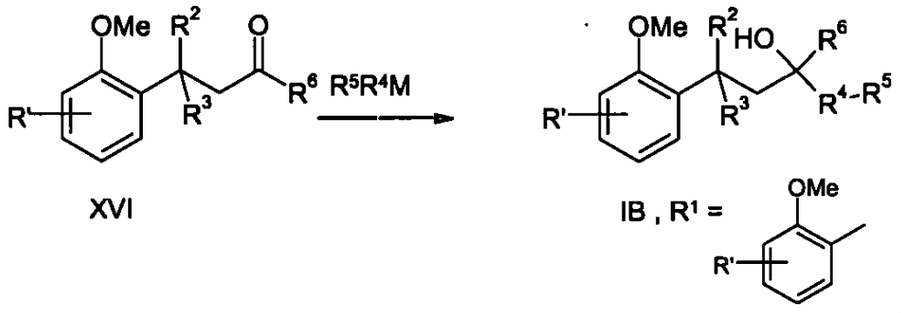
XIV XV ;

(c) hacer reaccionar la amida de Fórmula (XV) con un reactivo organometálico adecuado R^6M, en el que M es Li o MgX y X es Cl, Br o I, en un disolvente adecuado formando una cetona de Fórmula (XVI)



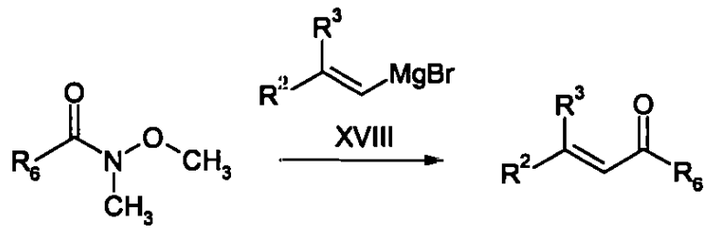
XV XVI ;

(d) hacer reaccionar la cetona de Fórmula (XVI) con un reactivo organometálico adecuado R^5R^4M en el que M es Li o MgX y X es Cl, Br o I, en un disolvente adecuado formando un compuesto de Fórmula (IB)



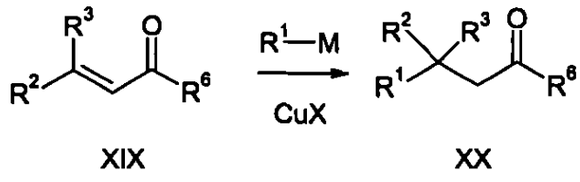
Un segundo procedimiento para preparar un compuesto de Fórmula (IB) comprende:

(a') hacer reaccionar una amida de Fórmula (XVII) con un bromuro de vinil magnesio que tiene R^2 y R^3 de Fórmula (XVIII) en un disolvente adecuado, proporcionando una enona de Fórmula (XIX)



;

(b') hacer reaccionar la enona de Fórmula (XIX) con un reactivo de organocobre adecuado generado a partir de un reactivo organometálico R^1M, en el que M es Li o MgX, y una sal de cobre CuX, en la que X es Cl, Br o I, en un disolvente adecuado, formando una cetona de Fórmula (XX)



; y

(c') hacer reaccionar la cetona de Fórmula (XX) con un reactivo organometálico adecuado R^5R^4M, en el que M es Li o MgX, y X es Cl, Br o I, en un disolvente adecuado, formando el compuesto de Fórmula (IB)



XX IB

En otro aspecto de la invención, los compuestos conforme a la invención se formulan en composiciones farmacéuticas que comprenden una cantidad eficaz, preferiblemente una cantidad farmacéuticamente eficaz, de un compuesto conforme a la invención o uno de sus tautómeros, profármacos, solvatos o sales, y un excipiente o vehículo farmacéuticamente aceptable.

La invención también proporciona un procedimiento para modular la función del receptor de glucocorticoides en un paciente, comprendiendo el procedimiento administrar a un paciente una cantidad eficaz de un compuesto conforme a la invención o uno de sus tautómeros, profármacos, solvatos o sales.

La invención proporciona además un procedimiento para tratar un estado de enfermedad o afección mediado por la función del receptor de glucocorticoides en un paciente que necesite dicho tratamiento, comprendiendo el procedimiento administrar al paciente una cantidad eficaz de un compuesto farmacéuticamente aceptable conforme a la invención o uno de sus tautómeros, profármacos, solvatos o sales.

Además, la invención proporciona también un procedimiento para tratar un estado de enfermedad o afección seleccionado de: diabetes tipo II, obesidad, enfermedades cardiovasculares, hipertensión, arteriosclerosis, enfermedades neurológicas, tumores suprarrenales y pituitarios y glaucoma, en un paciente que necesita dicho tratamiento, comprendiendo el procedimiento administrar al paciente una cantidad eficaz de un compuesto farmacéuticamente aceptable conforme a la invención o uno de sus tautómeros, profármacos, solvatos o sales.

La invención proporciona un procedimiento para tratar una enfermedad caracterizada por procesos inflamatorios, alérgicos o proliferativos, en un paciente que necesita dicho tratamiento, comprendiendo el procedimiento administrar al paciente una cantidad eficaz de un compuesto farmacéuticamente aceptable conforme a la invención o uno de sus tautómeros, profármacos, solvatos o sales. En una realización preferida de la invención, la enfermedad caracterizada por procesos inflamatorios, alérgicos o

proliferativos se selecciona de: (i) enfermedades del pulmón; (ii) enfermedades reumáticas o enfermedades autoinmunes o enfermedades de las articulaciones; (iii) enfermedades alérgicas; (iv) enfermedades por vasculitis; (v) enfermedades dermatológicas; (vi) enfermedades renales; (vii) enfermedades hepáticas; (viii) enfermedades gastrointestinales; (ix) enfermedades proctológicas; (x) enfermedades oculares; (xi) enfermedades del área del oído, nariz y garganta (ORL); (xii) enfermedades neurológicas; (xiii) enfermedades de la sangre; (xiv) enfermedades tumorales; (xv) enfermedades endocrinas; (xvi) enfermedades de trasplantes de órganos y tejidos y de injerto contra huésped; (xvii) estados severos de shock; (xviii) tratamiento de sustitución; y (xix) dolor de génesis inflamatoria. En otra realización preferida de la invención, la enfermedad caracterizada por procesos inflamatorios, alérgicos o proliferativos se selecciona de: diabetes tipo I, osteoartritis, síndrome de Guillain-Barre, restenosis después de angioplastia coronaria percutánea transluminal, enfermedad de Alzheimer, dolor agudo y crónico, aterosclerosis, lesión por reperfusión, enfermedades de resorción ósea, insuficiencia cardíaca congestiva, infarto de miocardio, lesión por calor, lesión en varios órganos secundaria a un traumatismo, meningitis purulenta aguda, enterocolitis necrotizante y síndromes asociados con hemodiálisis, leucoféresis y transfusión de granulocitos.

La invención proporciona además procedimientos para tratar los estados de enfermedad o trastornos citados antes, en un paciente que necesita dicho tratamiento, comprendiendo los procedimientos administrar de forma secuencial o simultánea al paciente: (a) una cantidad eficaz de un compuesto farmacéuticamente aceptable conforme a la invención o uno de sus tautómeros, profármacos, solvatos o sales; y (b) un glucocorticoide farmacéuticamente aceptable.

La invención proporciona además un procedimiento de ensayo de la función del receptor de glucocorticoides en una muestra, que comprende: (a) poner en contacto la muestra con una cantidad seleccionada de un compuesto conforme a la invención o uno de sus tautómeros, profármacos, solvatos o sales; y (b) detectar la cantidad de compuesto conforme a la invención o uno de sus tautómeros, profármacos, solvatos o sales unida a los receptores de glucocorticoides en la muestra. En una realización preferida de la invención, el compuesto conforme a la invención o uno de sus tautómeros, profármacos, solvatos o sales está marcado con un marcador detectable seleccionado de: un marcador radiactivo, un marcador fluorescente, un marcador quimioluminiscente, un cromóforo y un marcador de espín.

La invención también proporciona un procedimiento para visualizar la distribución del receptor de glucocorticoides en una muestra o paciente, comprendiendo el procedimiento: (a) poner en contacto la muestra o administrar al paciente un compuesto conforme a la invención o uno de sus tautómeros, profármacos, solvatos o sales que tenga un marcador detectable; (b) detectar la distribución espacial y la cantidad del compuesto conforme a la invención o uno de sus tautómeros, profármacos, solvatos o sales que tenga un marcador detectable unido a los receptores de glucocorticoides en la muestra o paciente usando un medio de visualización para obtener una imagen; y (c) presentar una imagen de la distribución espacial y la cantidad de compuesto conforme a la invención o uno de sus tautómeros, profármacos, solvatos o sales que tienen un marcador detectable unido a receptores de glucocorticoides en la muestra. En una realización preferida de la invención, el medio de visualización se selecciona de: radioescintigrafía, imagen por resonancia magnética nuclear (MRI), tomografía computerizada (barrido por CT), o tomografía por emisión de positrones (PET).

La invención también proporciona un kit para la determinación diagnóstica *in vitro* de la función del receptor de glucocorticoides en una muestra, que comprende: (a) una cantidad eficaz para el diagnóstico de un compuesto conforme a la invención o uno de sus tautómeros, profármacos, solvatos o sales; y (b) instrucciones para usar el kit de diagnóstico.

Descripción detallada de la invención

Definición de los términos y convenios usados

Los términos no definidos de forma específica en la presente memoria tendrán los significados que les daría un experto en la técnica a la vista de la descripción y el contexto. No obstante, tal y como se usa en la memoria descriptiva y en las reivindicaciones adjuntas, a no ser que se indique de otro modo, los siguientes términos tienen los significados indicados y se rigen por los siguientes convenios.

A. Términos y convenios de nomenclatura química

En los grupos, radicales o restos definidos a continuación, el número de átomos de carbono se especifica con frecuencia después del grupo, por ejemplo, alquilo C_1-C_{10} se refiere a un grupo alquilo o un radical que tiene 1 a 10 átomos de carbono. El término "inferior" aplicado a cualquier grupo que contenga carbonos se refiere a un grupo que contiene de 1 a 8 átomos de carbono, según sea lo apropiado para el grupo (es decir, un grupo cíclico deberá tener al menos 3 átomos para formar un anillo). En general, para grupos que comprenden dos o más subgrupos, el último grupo nombrado es el punto de

unión del radical, por ejemplo, "alquilarilo" se refiere a un radical monovalente de fórmula Alk-Ar-, mientras que "arilalquilo" se refiere a un radical monovalente de fórmula Ar-Alk- (siendo Alk un grupo alquilo y Ar un grupo Arilo). Por otro lado, el uso de un término que designe un radical monovalente en el que un radical divalente es apropiado se considerará que designa el radical divalente respectivo y *vice versa*. A no ser que se especifique de otro modo, se presuponen las definiciones convencionales de términos y valencias de átomos estables y se consiguen en todas las fórmulas y grupos.

Los términos "alquilo" o "grupo alquilo" se refieren a un radical monovalente hidrocarbonado alifático saturado de cadena ramificada o lineal. Este término se ejemplifica por grupos tales como metilo, etilo, *n*-propilo, 1-metiletilo (isopropilo), *n*-butilo, *n*-pentilo, 1,1-dimetiletilo (*terc*-butilo) y similares. Puede abreviarse como "Alk".

Los términos "alquenilo" o "grupo alquenilo" se refieren a un radical monovalente hidrocarbonado alifático de cadena ramificada o lineal que contiene al menos un doble enlace carbono-carbono. Este término se ejemplifica por grupos tales como etenilo, propenilo, *n*-butenilo, isobutenilo, 3-metilbut-2-enilo, *n*-pentenilo, heptenilo, octenilo, decenilo y similares.

Los términos "alquinilo" o "grupo alquinilo" se refieren a un radical monovalente hidrocarbonado alifático de cadena ramificada o lineal que contiene al menos un triple enlace carbono-carbono. Este término se ejemplifica por grupos tales como etinilo, propinilo, *n*-butinilo, 2-butinilo, 3-metilbutinilo, *n*-pentinilo, heptinilo, octinilo, decinilo y similares.

Los términos "alquileno" o "grupo alquileno" se refieren a un radical divalente hidrocarbonado alifático saturado de cadena ramificada o lineal que tiene el número especificado de átomos de carbono. Este término se ejemplifica por grupos tales como metileno, etileno, propileno, *n*-butileno y similares y puede representarse alternativamente en la presente memoria como -(alquil)-.

Los términos "alquenileno" o "grupo alquenileno" se refieren a un radical divalente hidrocarbonado alifático de cadena ramificada o lineal que tiene el número especificado de átomos de carbono y al menos un doble enlace carbono-carbono. Este término se ejemplifica por grupos tales como etenileno, propenileno, *n*-butenileno y similares, y se puede representar de forma alternativa y equivalente como -(alquilenil)-.

Los términos "alquinileno" o "grupo alquinileno" se refieren a un radical divalente hidrocarbonado alifático de cadena ramificada o lineal que tiene el número especificado de átomos de carbono y al menos un triple enlace carbono-carbono. Este término se ejemplifica por grupos tales como etinileno, propinileno, *n*-butinileno, 2-butinileno, 3-metilbutinileno, *n*-pentinileno, heptinileno, octinileno, decinileno y similares, y puede representarse de forma alternativa y equivalente como -(alquinil)-.

Los términos "alcoxi" o "grupo alcoxi" se refieren a un radical monovalente de fórmula AlkO-, en la que Alk es un grupo alquilo. Este término se ejemplifica por grupos tales como metoxi, etoxi, propoxi, isopropoxi, butoxi, *sec*-butoxi, *terc*-butoxi, pentoxi y similares.

Los términos "ariloxi", "grupo ariloxi", se refieren a un radical monovalente de fórmula ArO-, en la que Ar es arilo. Este término se ejemplifica por grupos tales como fenoxi, naftoxi y similares.

Los términos "alquilcarbonilo", "grupos alquilcarbonilo", "alcanoilo" o "grupos alcanoilo" se refieren a un radical monovalente de fórmula AlkC(O)-, en la que Alk es alquilo o hidrógeno.

Los términos "arilcarbonilo", "grupo arilcarbonilo", "aroilo" o "grupo aroilo" se refieren a un radical monovalente de fórmula ArC(O)-, en la que Ar es arilo.

Los términos "acilo" o "grupo acilo" se refieren a un radical monovalente de fórmula RC(O)-, en la que R es un sustituyente seleccionado de hidrógeno o un sustituyente orgánico. Sustituyentes ejemplo incluyen alquilo, arilo, arilalquilo, cicloalquilo, heterociclilo, heteroarilo, heteroarilalquilo y similares. Como tales, los términos comprenden grupos alquilcarbonilo y grupos arilcarbonilo.

Los términos "acilamino" o "grupo acilamino" se refieren a un radical monovalente de fórmula RC(O)N(R)-, en la que cada R es un sustituyente seleccionado de hidrógeno o un grupo sustituyente.

Los términos "alcoxicarbonilo" o "grupo alcoxicarbonilo" se refieren a un radical monovalente de fórmula AlkO-C(O)-, en la que Alk es alquilo. Grupos alcoxicarbonilo ejemplo incluyen metoxicarbonilo, etoxicarbonilo, *terc*-butiloxicarbonilo y similares.

Los términos "alquilaminocarboniloxi" o "grupo alquilaminocarboniloxi" se refieren a un radical monovalente de fórmula $R_2NC(O)O$-, en la que cada R es independientemente hidrógeno o alquilo inferior.

El término "alcoxicarbonilamino" o "grupo alcoxicarbonilamino" se refiere a un radical monovalente de fórmula ROC(O)NH-, en la que R es alquilo inferior.

Los términos "alquilcarbonilamino" o "grupo alquilcarbonilamino" o "alcanoilamino" o "grupos alcanoilamino" se refieren a un radical monovalente de fórmula AlkC(O)NH-, en la que Alk es alquilo. Grupos alquilcarbonilamino ejemplo incluyen acetamido ($CH_3C(O)NH$-).

Los términos "alquilaminocarboniloxi" o "grupo alquilaminocarboniloxi" se refieren a un radical monovalente de fórmula AlkNHC(O)O-, en la que Alk es alquilo.

Los términos "amino" o "grupo amino" se refieren a un grupo $-NH_2$.

Los términos "alquilamino" o "grupo alquilamino" se refieren a un radical monovalente de fórmula (Alk)NH-, en la que Alk es alquilo. Grupos alquilamino ejemplo incluyen metilamino, etilamino, propilamino, butilamino, *terc*-butilamino y similares.

Los términos "dialquilamino" o "grupo dialquilamino" se refieren a un radical monovalente de fórmula (Alk)(Alk)N-, en la que cada es independientemente alquilo. Grupos dialquilamino ejemplo incluyen dimetilamino, metiletilamino, dietilamino, dipropilamino, etilpropilamino y similares.

Los términos "amino sustituido" o "grupo amino sustituido" se refieren a un radical monovalente de fórmula $-NR_2$, en la que cada R independientemente es un sustituyente seleccionado de hidrógeno o los sustituyentes especificados (pero ambos R no pueden ser hidrógeno). Sustituyentes ejemplo incluyen alquilo, alcanoilo, arilo, arilalquilo, cicloalquilo, heterociclilo, heteroarilo, heteroarilalquilo y similares.

Los términos "alcoxicarbonilamino" o "grupo alcoxicarbonilamino" se refieren a un radical monovalente de fórmula AlkOC(O)NH-, en la que Alk es alquilo.

Los términos "ureido" o "grupo ureido" se refieren a un radical monovalente de fórmula

$R_2NC(O)NH$-, en la que cada R es independientemente hidrógeno o alquilo.

Los términos "halógeno" o "grupo halógeno" se refieren a un grupo fluoro, cloro, bromo o yodo.

El término "halo" se refiere a que uno o más átomos de hidrógeno del grupo están reemplazados con grupos halógeno.

Los términos "haloalquilo" o "grupo haloalquilo" se refieren a un radical monovalente hidrocarbonado alifático saturado de cadena ramificada o lineal, en el que uno o más átomos de hidrógeno del mismo están cada uno independientemente reemplazados con átomos de halógeno. Este término se ejemplifica por grupos tales como clorometilo, 1,2-dibromoetilo, 1,1,1-trifluoropropilo, 2-yodobutilo, 1-cloro-2-bromo-3-fluoropentilo y similares.

Los términos "sulfanilo", "grupo sulfanilo", "tioéter" o "grupo tioéter" se refieren a un radical divalente de fórmula -S-.

Los términos "alquiltio" o "grupo alquiltio" se refieren a un radical monovalente de fórmula AlkS-, en la que Alk es alquilo. Grupos ejemplo incluyen metiltio, etiltio, *n*-propiltio, isopropiltio, *n*-butiltio y similares.

Los términos "sulfonilo" o "grupo sulfonilo" se refieren a un radical divalente de fórmula $-SO_2-$.

Los términos "sulfonilamino" o "grupo sulfonilamino" se refieren a un radical divalente de fórmula $-SO_2NR-$, en la que R es un hidrógeno o un grupo sustituyente.

Los términos "aminosulfonilo" o "grupo aminosulfonilo" se refieren a un radical monovalente de fórmula NR_2SO_2-, en la que cada R es independientemente hidrógeno o un grupo sustituyente.

Los términos "carbociclo" o "grupo carbocíclico" se refieren a un radical monovalente o divalente monocíclico o policíclico de 3 a 15 miembros alifático estable formado únicamente por átomos de carbono e hidrógeno que puede comprender uno o más anillos condensados o con puente, preferiblemente un anillo monocíclico de 5 a 7 miembros o bicíclico de 7 a 10 miembros. A no ser que se indique de otro modo, el

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carbociclo puede estar unido en cualquier átomo de carbono que origine una estructura estable y , si está sustituido, puede estar sustituido en cualquier átomo de carbono adecuado que origine una estructura estable. El término comprende cicloalquilo (incluyendo espirocicloalquilo), cicloalquileno, cicloalquenilo, cicloalquenileno, cicloalquinilo y cicloalquinileno y similares.

Los términos "cicloalquilo" o grupo "cicloalquilo" se refieren a un radical monovalente monocíclico o policíclico de 3 a 15 miembros alifático saturado estable formado únicamente por átomos de carbono e hidrógeno que puede comprender uno o más anillos condensados o con puente, preferiblemente un anillo monocíclico de 5 a 7 miembros o bicíclico de 7 a 10 miembros. A no ser que se indique de otro modo, el anillo cicloalquilo puede estar unido en cualquier átomo de carbono que origine una estructura estable y, si está sustituido, puede estar sustituido en cualquier átomo de carbono adecuado que origine una estructura estable. Grupos cicloalquilo ejemplo incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo, ciclononilo, ciclodecilo, norbornanilo, adamantilo, tetrahidronaftilo (tetralina), 1-decalinilo, biciclo[2.2.2]octanilo, 1-metilciclopropilo, 2-metilciclopentilo, 2-metilciclooctilo y similares.

Los términos "cicloalquenilo" o "grupo cicloalquenilo" se refieren a un radical monovalente monocíclico o policíclico de 3 a 15 miembros alifático estable que tiene al menos un doble enlace carbono-carbono y está formado únicamente de átomos de carbono e hidrógeno que puede comprender uno o más anillos condensados o con puente, preferiblemente un anillo monocíclico de 5 a 7 miembros o bicíclico de 7 a 10 miembros. A no ser que se indique de otro modo, el anillo cicloalquenilo puede estar unido en cualquier átomo de carbono que origine una estructura estable y, si está sustituido, puede estar sustituido en cualquier átomo de carbono que origine una estructura estable. Grupos cicloalquenilo estables incluyen ciclopentenilo, ciclohexenilo, cicloheptenilo, ciclooctenilo, ciclononenilo, ciclodecenilo, norbornenilo, 2-metilciclopentenilo, 2-metilciclooctenilo y similares.

Los términos "cicloalquinilo" o "grupo cicloalquinilo" se refieren a un radical monovalente monocíclico o policíclico de 8 a 15 miembros alifático estable que tiene al menos un triple enlace carbono-carbono y está formado únicamente de átomos de carbono e hidrógeno que puede comprender uno o más anillos condensados o con puente, preferiblemente un anillo monocíclico de 8 a 10 miembros o bicíclico de 12 a 15 miembros. A no ser que se indique lo contrario, el anillo cicloalquinilo puede estar

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sustituido en cualquier átomo de carbono que origine una estructura estable y, si está sustituido, puede estar sustituido en cualquier átomo de carbono que origine una estructura estable. Grupos cicloalquinilo ejemplo incluyen ciclooctinilo, ciclononinilo, ciclodecinilo, 2-metilciclooctinilo y similares.

Los términos "cicloalquileno" o "grupo cicloalquileno" se refieren a un radical divalente monocíclico o policíclico de 3 a 15 miembros alifático saturado estable formado únicamente de átomos de carbono e hidrógeno que puede comprender uno o más anillos condensados o con puente, preferiblemente un anillo monocíclico de 5 a 7 miembros o bicíclico de 7 a 10 miembros. A no ser que se indique lo contrario, el anillo cicloalquilo puede estar unido en cualquier átomo de carbono que origine una estructura estable y, si está sustituido, puede estar sustituido en cualquier átomo de carbono que origine una estructura estable. Grupos cicloalquileno estables incluyen ciclopentileno y similares.

Los términos "cicloalquenileno" o "grupo cicloalquenileno" se refieren a un radical divalente monocíclico o policíclico de 5 a 15 miembros alifático estable que tiene al menos un doble enlace carbono-carbono y está formado únicamente de átomos de carbono e hidrógeno que puede comprender uno o más anillos condensados o con puente, preferiblemente, un anillo monocíclico de 5 a 7 miembros o bicíclico de 7 a 10 miembros. A no ser que se indique de otro modo, el anillo cicloalquenileno puede estar unido en cualquier átomo de carbono que origine una estructura estable y, si está sustituido, puede estar sustituido en cualquier átomo de carbono que origine una estructura estable. Grupos cicloalquenileno ejemplo incluyen ciclopentenileno, ciclohexenileno, cicloheptenileno, ciclooctenileno, ciclononenileno, ciclodecenileno, norbornenileno, 2-metilciclopentenileno, 2-metilciclooctenileno y similares.

Los términos "cicloalquinileno" o "grupo cicloalquinileno" se refiere a un radical divalente monocíclico o policíclico de 8 a 15 miembros alifático estable que tiene al menos un triple enlace carbono-carbono y está formado únicamente de átomos de carbono e hidrógeno que puede comprender uno o más anillos condensados o con puente, preferiblemente un anillo monocíclico de 8 a 10 miembros o bicíclico de 12 a 15 miembros. A no ser que se indique de otro modo, el anillo cicloalquinileno puede estar unido en cualquier átomo de carbono que origine una estructura estable y, si está sustituido, puede estar sustituido en cualquier átomo de carbono que origine una estructura estable. Grupos cicloalquinileno estables incluyen ciclooctinileno, ciclononinileno, ciclodecinileno, 2-metilciclooctinileno y similares.

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Los términos "arilo" o "grupo arilo" se refieren a un radical monovalente o divalente carbocíclico aromático de 6 a 14 átomos de carbono que tiene un anillo sencillo (por ejemplo, fenilo o fenileno) o varios anillos condensados (por ejemplo, naftilo o antranilo). A no ser que se indique de otro modo, el anillo arilo puede estar unido en cualquier átomo de carbono adecuado que origine una estructura estable y, si está sustituido, puede estar sustituido en cualquier átomo de carbono que origine una estructura estable. Grupos arilo ejemplo incluyen fenilo, naftilo, antrilo, fenantrilo, indanilo, indenilo, bifenilo y similares. Puede abreviarse como "Ar".

Los términos "heteroarilo" o "grupo heteroarilo" se refieren a un radical monovalente o divalente monocíclico o policíclico de 5 a 14 miembros aromático estable que puede comprender uno o más anillos condensados o con puente, preferiblemente un radical monocíclico de 5 a 7 miembros o bicíclico de 7 a 10 miembros, que tiene de uno a cuatro heteroátomos en el anillo o anillos, seleccionados independientemente de nitrógeno, oxígeno y azufre, pudiendo estar cualquier heteroátomo azufre opcionalmente oxidado y pudiendo estar cualquier heteroátomo nitrógeno opcionalmente oxidado o cuaternarizado. A no ser que se indique de otro modo, el anillo heteroarilo puede estar unido en cualquier heteroátomo o átomo de carbono adecuado que origine una estructura estable y, si está sustituido, puede estar sustituido en cualquier heteroátomo o átomo de carbono que origine una estructura estable. Heteroarilos ejemplo y preferidos furanilo, tienilo, pirrolilo, oxazolilo, tiazolilo, imidazolilo, pirazolilo, isoxazolilo, isotiazolilo, oxadiazolilo, triazolilo, tetrazolilo, tiadiazolilo, piridinilo, piridazinilo, pirimidinilo, pirazinilo, triazinilo, indolizinilo, azaindolizinilo, indolilo, azaindolilo, diazaindolilo, dihidroindolilo, dihidroazaindolilo, isoindolilo, azaisoindolilo, benzofuranilo, furanopiridinilo, furanopirimidinilo, furanopirazinilo, furanopiridazinilo, dihidrobenzofuranilo, dihidrofuranopiridinilo, dihidrofuranopirimidinilo, benzodioxolanilo, benzotienilo, tienopiridinilo, tienopirimidinilo, tienopirazinilo, tienopiridazinilo, dihidrobenzotienilo, dihidrotienopiridinilo, dihidrotienopirimidinilo, indazolilo, azaindazolilo, diazaindazolilo, bencimidazolilo, imidazopiridinilo, benzotiazolilo, tiazolopiridinilo, tiazolopirimidinilo, benzoxazolilo, oxazolopiridinilo, oxazolopirimidinilo, benzoisoxazolilo, purinilo, cromanilo, azacromanilo, quinolizinilo, quinolinilo, dihidroquinolinilo, tetrahidroquinolinilo, isoquinolinilo, dihidroisoquinolinilo, tetrahidroisoquinolinilo, cinolinilo, azacinolinilo, ftalazinilo, azaftalazinilo, quinazolinilo, azaquinazolinilo, quinoxalinilo, azaquinoxalinilo, naftiridinilo, dihidronaftiridinilo, tetrahidronaftiridinilo, pteridinilo, carbazolilo, acridinilo,

fenazinilo, fenotiazinilo y fenoxazinilo y similares.

Los términos "heterociclo", "grupo heterociclo", "heterociclilo" o "grupo heterociclilo" se refieren a un anillo monovalente o divalente, monocíclico o policíclico de 5 a 14 miembros no aromático estable, que puede comprender uno o más anillos condenados o con puente, preferiblemente, un anillo monocíclico de 5 a 7 miembros o bicíclico de 7 a 10 miembros, que tiene de uno a tres heteroátomos en el anillo, seleccionados independientemente de nitrógeno, oxígeno y azufre, pudiendo estar cualquier heteroátomo azufre opcionalmente oxidado y pudiendo estar cualquier heteroátomo nitrógeno opcionalmente oxidado o cuaternarizado. A no ser que se indique de otro modo, el anillo heterociclilo puede estar unido en cualquier heteroátomo o átomo de carbono adecuado que origine una estructura estable y, si está sustituido, puede estar sustituido en cualquier heteroátomo o átomo de carbono adecuado que origine una estructura estable. Heterociclos ejemplo y preferidos incluyen pirrolinilo, pirrolidinilo, pirazolinilo, pirazolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, tetrahidropiranilo, tetrahidrotiopiranilo, tetrahidrofuranilo, hexahidropirimidinilo, hexahidropiridazinilo y similares.

La expresión "compuestos de fórmula (I)" y las expresiones equivalentes incluirán cualquiera o ambos compuestos de Fórmula (IA) y compuestos de Fórmula (IB) cuando el contexto lo permita.

El término "compuestos de la invención" y expresiones equivalentes incluirán compuestos de Fórmula (I) como se ha descrito en la presente memoria, incluyendo sus tautómeros, los profármacos, las sales, en particular las sales farmacéuticamente aceptables y los solvatos e hidratos de los mismos, cuando el contexto así lo permita. En general y de forma preferida, se sobreentiende que los compuestos de la invención y las fórmulas que designan los compuestos de la invención incluyen solo compuestos estables de los mismos y excluyen compuestos inestables, incluso si pudiera considerarse un compuesto inestable que está literalmente incluido por la fórmula del compuesto. De igual forma, las referencias a intermedios, estén o no reivindicados explícitamente, se refiere a la inclusión de sus sales y solvatos, cuando el contexto así lo permita. Por motivos de claridad, algunas veces se indican en este texto ejemplos particulares cuando el contexto así lo permita, pero estos casos son meramente ilustrativos y no se deben excluir otros casos cuando el contexto lo permita.

Los términos "opcional" u "opcionalmente" se refieren a que el suceso o circunstancias

descritas seguidamente pueden ocurrir o no, y que la descripción incluye casos en los que el suceso ocurre y casos en los que no ocurre. Por ejemplo, "arilo opcionalmente sustituido" significa que el radical arilo puede o no estar sustituido y que la descripción incluye tanto los radicales arilo sustituidos como los radicales arilo que no están sustituidos.

Los términos "compuesto estable" o "estructura estable" se refieren a un compuesto que es suficientemente robusto para superar el aislamiento hasta un grado útil de pureza a partir de una mezcla de reacción y la formulación en un agente terapéutico o de diagnóstico eficaz. Por ejemplo, un compuesto que tenga una "valencia libre" o es un carbanión no es un compuesto contemplado por la invención.

El término "sustituido" se refiere a que uno o más hidrógenos cualesquiera en un átomo de un grupo o resto, esté o no designado de forma específica, está reemplazado con una selección del grupo indicado de sustituyentes, con la condición de que no se supere la valencia normal del átomo y que la sustitución origine un compuesto estable. Si un enlace a un sustituyente se muestra cruzando el enlace que conecta dos átomos en un anillo, entonces dicho sustituyente puede estar unido en cualquier átomo del anillo. Cuando un sustituyente se presenta sin indicar el átomo mediante el cual dicho sustituyente está unido al resto del compuesto, entonces dicho sustituyente puede estar unido a través de cualquier átomo de dicho sustituyente. Por ejemplo, cuando un sustituyente es piperazinilo, piperidinilo o tetrazolilo, a no ser que se indique de otro modo, dicho grupo piperazinilo, piperidinilo o tetrazolilo puede estar unido al resto del compuesto de la invención a través de cualquier átomo en dicho grupo piperazinilo, piperidinilo o tetrazolilo. Por lo general, cuando cualquier sustituyente o grupo aparece más de una vez en cualquier sustituyente o compuesto, su definición en cada caso es independiente de su definición en cada uno de los otros casos. Así, por ejemplo, si se muestra que un grupo está sustituido con 0 a 2 R^5, entonces dicho grupo está opcionalmente sustituido con hasta dos grupos R^5 y R^5 en cada caso se selecciona independientemente de la lista definida de posibles R^5. No obstante, dichas combinaciones de sustituyentes y/o variables, son posibles solo si dichas combinaciones originan compuestos estables.

En una realización específica, el término "aproximadamente" significa entorno al 20%, preferiblemente 10% y más preferiblemente 5% de un valor o intervalo dado.

El rendimiento de cada una de las reacciones descritas en la presente memoria está

expresado como porcentaje del rendimiento teórico.

B. Términos y convenios para sal, profármaco, derivado y solvato

Los términos "profármaco" o "derivado profármaco" se refieren a un derivado o vehículo unido covalentemente del compuesto principal o sustancia farmacológica activa que sufre al menos una biotransformación antes de mostrar sus efectos farmacológicos. En general, tales profármacos tienen grupos metabólicamente lábiles y se transforman rápidamente *in vivo* proporcionando el compuesto principal, por ejemplo, por hidrólisis en la sangre y, por lo general, incluyen análogos ésteres y amida de los compuestos principales. Los profármacos se formulan con el objeto de mejorar la estabilidad química, mejorar la aceptación y cumplimiento terapéutico del paciente, mejorar la biodisponibilidad, duración prolongada de la acción, mejorar la selectividad por un órgano, mejorar la formulación (por ejemplo, mayor solubilidad en agua) y/o reducir los efectos secundarios (por ejemplo, toxicidad). En general, los propios profármacos tienen una actividad biológica débil o nula y son estables en condiciones normales. Los profármacos se pueden preparar fácilmente a partir de los compuestos principales usando procedimientos conocidos en la técnica, tales como los descritos en A Textbook of Drug Design and Development, Krogsgaard-Larsen and H. Bundgaard (eds.), Gordon & Breach, 1991, en particular, el capítulo 5: "Design and Applications of Prodrugs"; Design of Prodrugs, H. Bundgaard (ed.), Elsevier, 1985; Prodrugs: Topical and Ocular Drug Delivery, K.B. Sloan (ed.), Marcel Dekker, 1998; Methods in Enzymology, K. Widder *et al.* (eds.), Vol. 42, Academic Press, 1985, en particular, las páginas 309-396; Burger's Medicinal Chemistry and Drug Discovery, 5ª Ed., M. Wolff (ed.), John Wiley & Sons, 1995, en particular el Vol. 1 y las páginas 172-178 y las páginas 949-982; Pro-Drugs as Novel Delivery Systems, T. Higuchi and V. Stella (eds.), Am. Chem. Soc., 1975; Bioreversible Carriers in Drug Design, E.B. Roche (ed.), Elsevier, 1987, cada una de las cuales se incorpora en la presente memoria como referencia en su totalidad.

El término "profármaco farmacéuticamente aceptable" tal y como se usa en la presente memoria, se refiere a un profármaco de un compuesto de la invención que, dentro del alcance del criterio médico, es adecuado para usar en contacto con los tejidos de seres humanos y animales inferiores sin una toxicidad, irradiación, respuesta alérgica y respuestas similares indeseadas, proporcional con una relación beneficio/riesgo razonable y es eficaz para su uso deseado, así como las formas híbridas, cuando son posibles.

El término "sal" se refiere a una forma iónica del compuesto principal o el producto de la reacción entre el compuesto principal con un ácido o base adecuado para preparar la sal de ácido o sal de base del compuesto principal. Las sales de los compuestos de la presente invención se pueden sintetizar a partir de los compuestos principales que contienen un resto básico o ácido por métodos químicos convencionales. Por lo general, las sales se preparan haciendo reaccionar el compuesto principal base libre o ácido libre con cantidades estequiométricas o con un exceso del ácido o base inorgánico u orgánico formador de la sal deseado, en un disolvente adecuado o en diversas combinaciones de disolventes.

El término "sal farmacéuticamente aceptable" se refiere a una sal de un compuesto de la invención que, dentro del alcance del criterio médico habitual, es adecuada para usar en contacto con tejidos de seres humanos y animales inferiores sin una toxicidad, irritación, respuesta alérgica o respuesta indeseada similar, proporcional a una relación beneficio/riesgo razonable, por lo general soluble o dispersable en agua o aceite, y eficaz para su uso deseado. El término incluye sales de adición de ácidos farmacéuticamente aceptables y sales de adición de bases farmacéuticamente aceptables. Como los compuestos de la presente invención son útiles tanto en forma de base libre como de sal, en la práctica, el uso de la forma de sal equivale al uso de la forma de base. Por ejemplo, en S.M. Birge *et al.*, J. Pharm. Sci., 1977, 66, págs. 1-19, que se incorpora en la presente memoria como referencia en su totalidad, se encuentran listas de sales adecuadas.

El término "sal de adición de ácidos farmacéuticamente aceptable" se refiere a las sales que mantienen la eficacia y propiedades biológicas de las bases libres y que no son biológicamente o de cualquier otro modo indeseables, formadas con ácidos inorgánicos tales como ácido clorhídrico, ácido bromhídrico, ácido yodhídrico, ácido sulfúrico, ácido sulfámico, ácido nítrico, ácido fosfórico y similares, y ácidos orgánicos tales como ácido acético, ácido tricloroacético, ácido tribromoacético, ácido adípico, ácido algínico, ácido ascórbico, ácido aspártico, ácido bencenosulfónico, ácido benzoico, ácido 2-acetoxibenzoico, ácido butírico, ácido canfórico, ácido canfosulfónico, ácido cinámico, ácido cítrico, ácido diglucónico, ácido etanosulfónico, ácido glutámico, ácido glicólico, ácido glicerofosfórico, ácido hemisúlfico, ácido heptanoico, ácido hexanoico, ácido fórmico, ácido fumárico, ácido 2-hidroxietanosulfónico (ácido isetiónico), ácido láctico, ácido maleico, ácido hidroximaleico, ácido málico, ácido malónico, ácido mandélico, ácido mesitilenosulfónico, ácido metanosulfónico, ácido naftalenosulfónico, ácido nicotínico, ácido 2-naftalenosulfónico, ácido oxálico, ácido pamoico, ácido

pectínico, ácido fenilacético, ácido 3-fenilpropiónico, ácido pícrico, ácido piválico, ácido propanoico, ácido pirúvico, ácido salicílico, ácido esteárico, ácido succínico, ácido sulfámico, ácido tartárico, ácido *p*-toluensulfónico, ácido undecanoico y similares.

El término "sal de adición de bases farmacéuticamente aceptable" se refiere a las sales que mantienen la eficacia y propiedades biológicas de los ácidos libres y que no son biológicamente o de cualquier otro modo indeseables, formadas con bases inorgánicas tales como amoníaco o hidróxido, carbonato, o bicarbonato de amonio o un catión metálico tal como sodio, potasio, litio, calcio, magnesio, hierro, cinc, cobre, manganeso, aluminio y similares. Son particularmente preferidas las sales de amonio, potasio, sodio, calcio y magnesio. Las sales derivadas de bases no tóxicas orgánicas farmacéuticamente aceptables incluyen sales de aminas primarias, secundarias y terciarias, compuestos de amina cuaternarios, aminas sustituidas incluyendo las aminas sustituidas naturales, aminas cíclicas y resinas de intercambio iónico básicas tales como metilamina, dimetilamina, trimetilamina, etilamina, dietilamina, trietilamina, isopropilamina, tripropilamina, tributilamina, etanolamina, dietanolamina, 2-dimetilaminoetanol, 2-dietilaminoetanol, diciclohexilamina, lisina, arginina, histidina, cafeína, hidrabamina, colina, betaína, etilenodiamina, glucosamina, metilglucamina, teobromina, purinas, piperazina, piperidina, *N*-etilpiperidina, compuestos de tetrametilamonio, compuestos de tetraetilamonio, piridina, *N,N*-dimetilanilina, *N*-metilpiperidina, *N*-metilmorfolina, diciclohexilamina, dibencilamina, *N,N*-dibencilfenetilamina, 1-efenamina, *N,N'*-dibenciletilendiamina, resinas de poliaminas y similares. Las bases no tóxicas orgánicas particularmente preferidas son isopropilamina, dietilamina, etanolamina, trimetilamina, diciclohexilamina, colina y cafeína.

El término "solvato" se refiere a una asociación física de un compuesto con una o más moléculas de disolvente o un complejo de estequiometría variable formado por un soluto (por ejemplo, un compuesto de Fórmula (I)) y un disolvente, por ejemplo, agua, etanol o ácido acético. Esta asociación física puede implicar diversos grados de unión iónica o covalente, incluyendo el enlace de hidrógeno. En ciertos casos, el solvato podrá aislarse, por ejemplo, cuando una o más moléculas de disolvente estén incorporadas en la red cristalina del sólido cristalino. En general, los disolventes seleccionados no interfieren con la actividad biológica del soluto. Los solvatos incluyen tanto solvatos en fase en solución como los aislables. Solvatos representativos incluyen hidratos, etanolatos, metanolatos y similares.

El término "hidrato" se refiere a un solvato en el que la(s) molécula(s) de disolvente

es/son H_2O.

Los compuestos de la presente invención tal y como se describen a continuación incluyen la base libre o su ácido, sus sales, solvatos y profármacos y pueden incluir átomos de azufre oxidados o átomos de nitrógeno cuaternarizados en su estructura, aunque no se exponga o muestra de forma explícita, en particular las formas farmacéuticamente aceptables de los mismos. Se desea que tales formas, en particular, las formas farmacéuticamente aceptables, estén incluidas en las reivindicaciones adjuntas.

C. Términos y convenios para los isómeros

El término "isómeros" se refiere a compuestos que tienen el mismo número y tipo de átomos y, por ello, el mismo peso molecular, pero se diferencian con respecto a la disposición o configuración de los átomos en el espacio. El término incluye estereoisómeros e isómeros geométricos.

Los términos "estereoisómero" o "isómero óptico" se refieren a un isómero estable que tiene al menos un átomo quiral o rotación restringida que da lugar a planos de asimetría perpendiculares (por ejemplo, ciertos bifenilos, alenos y espirocompuestos) y pueden rotar la luz polarizada en el plano. Debido a que existen centros asimétricos y otras estructuras químicas en los compuestos de la invención que pueden dar lugar a estereoisomería, la invención contempla los estereoisómeros y sus mezclas. Los compuestos de la invención y sus sales incluyen átomos de carbono asimétricos y por tanto, pueden existir como estereoisómeros individuales, racematos y mezclas de enantiómeros y diastereoisómeros. De forma típica, tales compuestos se prepararán como una mezcla racémica. No obstante, si se desea, tales compuestos se pueden preparar o aislar como estereoisómeros puros, es decir, como enantiómeros o diastereoisómeros individuales o como mezclas enriquecidas en un estereoisómero. Como se describe más adelante con más detalle, los estereoisómeros individuales de compuestos se preparan por síntesis a partir de materiales de partida ópticamente activos que contienen los centros quirales deseados o preparando mezclas de productos enantioméricos seguido por separación o resolución, tal como conversión en una mezcla de diastereoisómeros seguida por separación o recristalización, técnicas cromatográficas, uso de agentes de resolución quirales o separación directa de los enantiómeros en columnas cromatográficas quirales. Los materiales de partida de estereoquímica particular están disponibles de forma comercial o se preparan por procedimientos descritos a continuación y se resuelven por procedimientos bien

conocidos en la técnica.

El término "enantiómeros" se refiere a una pareja de estereoisómeros que son imágenes especulares no superponibles entre sí..

Los términos "diastereoisómeros" o "diastereómeros" se refieren a isómeros ópticos que no son imágenes especulares entre sí.

Los términos "mezcla racémica" o "racemato" se refieren a una mezcla que contiene partes iguales de los enantiómeros individuales.

El término "mezcla no racémica" se refiere a una mezcla que contiene partes desiguales de los enantiómeros individuales.

El término "isómero geométrico" se refiere a un isómero estable que se origina de una libertad restringida de rotación alrededor de dobles enlaces (por ejemplo, *cis*-2-buteno y *trans*-2-buteno) o en una estructura cíclica (por ejemplo, *cis*-1,3-diclorociclobutano y *trans*-1,3-diclorociclobutano). Debido a que en los compuestos de la invención pueden estar presentes dobles enlaces carbono-carbono (olefínicos), dobles enlaces C=N, estructuras cíclicas y similares, la invención contempla cada una de los diversos isómeros geométricos estables y sus mezclas resultantes de la disposición de sustituyentes alrededor de estos dobles enlaces y en estas estructuras cíclicas. Los sustituyentes y los isómeros se designan usando el convenio *cis/trans* o usando el sistema *E* o *Z*, en el que el término "*E*" se refiere a sustituyentes de orden mayor en lados opuestos del doble enlace y el término "*Z*" se refiere a sustituyentes de orden mayor en el mismo lado del doble enlace. En J. March, Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 4ª ed., John Wiley & Sons, 1992, que se incorpora en la presente memoria como referencia en su totalidad, se puede encontrar una descripción detallada de la isomería *E* y *Z*. Algunos de los siguientes ejemplos representan isómeros *E* individuales, isómeros *Z* individuales y mezclas de isómeros *E/Z*. La determinación de los isómeros *E* y *Z* se puede realizar por procedimientos analíticos tales como cristalografía de rayos x, RMN de ^{1}H y RMN de ^{13}C.

Algunos de los compuestos de la invención pueden existir en más de un forma tautómera. Como se ha citado antes, los compuestos de la invención incluyen también todos los citados tautómeros.

Es bien conocido en la técnica que la actividad biológica y farmacológica de un compuesto es sensible a la estereoquímica del compuesto. Así, por ejemplo, los enantiómeros presentan con frecuencia una actividad biológica marcadamente diferente que incluye diferencias en las propiedades farmacocinéticas, incluyendo el metabolismo, unión a proteínas y similares, y en las propiedades farmacológicas, incluyendo el tipo de actividad mostrada, el grado de actividad, toxicidad y similares. Así, un experto en la técnica apreciará que un enantiómero puede ser más activo o puede mostrar efectos beneficiosos cuando esté enrriquecido con respecto al otro enantiómero o cuando esté separado del otro enantiómero. Además, a partir de esta descripción y de los conocimientos de la técnica anterior, un experto en la técnica conocerá la forma de separar, enrriquecer o preparar de forma selectiva los enantiómeros de los compuestos de la invención .

Así, aunque puede usarse la forma racémica del fármaco, con frecuencia es menos eficaz que administrar una cantidad igual del fármaco enantioméricamente puro; de hecho, en algunos casos, un enantiómero puede ser farmacológicamente inactivo y simplemente serviría como mero diluyente. Por ejemplo, aunque el ibuprofeno se ha administrado anteriormente como racemato, se ha demostrado que solo el isómero *S* del ibuprofeno es eficaz como agente antiinflamatorio (en el caso del ibuprofeno, no obstante, aunque el isómero *R* es inactivo, se convierte *in vivo* en el isómero *S*, así, la rapidez de la acción de la forma racémica del fármaco es menor que la del isómero *S* puro). Por otro lado, las actividades farmacológicas de enantiómeros pueden tener actividad biológica diferenciada. Por ejemplo, la *S*-penicilamina es un agente terapéutico para la artritis crónica, mientras que la *R*-penicilamina es tóxica. De hecho, algunos enantiómeros purificados tienen ventajas sobre los racematos, ya que se ha descrito que isómeros individuales purificados tienen velocidades de penetración transdérmica más rápidas comparadas con las de la mezcla racémica. Véanse las patentes de Estados Unidos números 5.114.946 y 4.818.541.

Así, si un enantiómero es farmacológicamente más activo, menos tóxico o tiene una disposición preferida en el cuerpo que el otro enantiómero, será terapéuticamente más beneficioso administrar dicho enantiómero preferentemente. De este modo, el paciente sometido a tratamiento estaría expuesto a una menor dosis total del fármaco y a una menor dosis de un enantiómero que es posiblemente tóxico o un inhibidor del otro enantiómero.

La preparación de enantiómeros puros o mezclas de excesos enantioméricos (ee) o

pureza enantiomérica deseados se lleva a cabo por uno o más de los muchos procedimientos de (a) separación o resolución de enantiómeros, o (b) síntesis enantioselectiva conocida por los expertos en la técnica, o una combinación de los mismos. Estos procedimientos de resolución se basan por lo general en el reconocimiento quiral e incluyen, por ejemplo, cromatografía usando fases estacionarias quirales, complejación hospedador-huésped enantioselectiva, resolución o síntesis usando compuestos auxiliares quirales, síntesis enantioselectiva, resolución cinética enzimática y no enzimática, o cristalización enantioselectiva espontánea. Dichos procedimientos se describen generalmente en Chiral Separation Techniques: A Practical Approach (2nd Ed.), G. Subramanian (ed.), Wiley-VCH, 2000; T.E. Beesley and R.P.W. Scott, Chiral Cromatography, John Wiley & Sons, 1999; y Satinder Ahuja, Chiral Separations by Cromatography, Am. Chem. Soc., 2000. Por otro lado, existen igualmente procedimientos conocidos para la cuantificación del exceso o pureza enantiomérica, por ejemplo, GC, HPLC, CE o RMN, y para la asignación de la configuración absoluta y conformación, por ejemplo, CD ORD, cristalografía por rayos x o RMN.

En general, se incluyen todas las formas tautómeras y formas isoméricas y mezclas, ya sean isómeros geométricos individuales o estereoisómeros o mezclas racémicas o no racémicas, de una estructura o compuesto químico, a no ser que se indique de forma específica en el nombre del compuesto o estructura la estereoquímica o forma isomérica específica.

D. Términos y convenios sobre administración de fármacos y diagnóstico y tratamiento

El término "paciente" incluye a los seres humanos y a los animales no humanos.

El término "cantidad eficaz" se refiere a una cantidad de un compuesto conforme a la invención que, en el contexto que se está administrando o usando, es suficiente para conseguir el efecto o resultado deseado. Dependiendo del contexto, el término cantidad eficaz puede incluir sinónimos con una cantidad farmacéuticamente eficaz o una cantidad eficaz para el diagnóstico.

Los términos "cantidad farmacéuticamente eficaz" o "cantidad terapéuticamente eficaz" se refieren a una cantidad de un compuesto conforme a la invención que, cuando se administra a un paciente que lo necesita, es suficiente para efectuar el tratamiento de

estados de enfermedad, trastornos o afecciones para los cuales tienen utilidad los compuestos. Dicha cantidad será suficiente para obtener una respuesta biológica o médica de un tejido, sistema o paciente que se esté buscando por el médico o investigador. La cantidad de compuesto conforme a la invención que constituye una cantidad terapéuticamente eficaz variará dependiendo de factores tales como el compuesto y su actividad biológica, la composición usada para administración, el tiempo de administración, la vía de administración, la velocidad de excreción del compuesto, la duración del tratamiento, el tipo de estado de enfermedad o trastorno que se esté tratando y su intensidad, los fármacos usados en combinación con o coincidentemente con los compuestos de la invención y la edad, peso corporal, estado de salud general, sexo y dieta del paciente. Dicha cantidad terapéuticamente eficaz se puede determinar de forma rutinaria por un experto en la técnica con ayuda de su conocimiento, la técnica anterior y esta descripción.

El término "cantidad eficaz para el diagnóstico" se refiere a una cantidad de un compuesto conforme a la invención que, cuando se usa en un procedimiento, aparato o ensayo de diagnóstico, es suficiente para conseguir el efecto de diagnóstico deseado o la actividad biológica deseada necesaria para el procedimiento, aparato o ensayo de diagnóstico. Dicha cantidad será suficiente para producir la respuesta médica o biológica en un procedimiento, aparato o ensayo de diagnóstico, que puede incluir una respuesta biológica o médica en un paciente o en un tejido o sistema *in vitro* o *in vivo*, que se pretenda por el médico o investigador. La cantidad de un compuesto conforme a la invención que constituye una cantidad eficaz para el diagnóstico variará dependiendo de factores tales como el compuesto y su actividad biológica, el procedimiento, aparato o ensayo de diagnóstico, la composición usada para administración, el tiempo de administración, la vía de administración, la velocidad de excreción del compuesto, la duración del tratamiento, los fármacos y otros compuestos usados en combinación con o coincidentemente con los compuestos de la invención y, si el paciente es el sujeto de la administración para el diagnóstico, la edad, peso corporal, estado de salud general, sexo y dieta del paciente. Dicha cantidad eficaz para el diagnóstico se puede determinar de forma rutinaria por un experto en la técnica con ayuda de su conocimiento, la técnica anterior y esta descripción.

El término "modular" se refiere a la capacidad de un compuesto de alterar la función del receptor de glucocorticoides, por ejemplo, uniéndose a, y estimulando o inhibiendo las respuestas funcionales del receptor de glucocorticoides.

El término "modulador" en el contexto de describir los compuestos conforme a la invención se refiere a un compuesto que modula la función del receptor de glucocorticoides. Como tales, dichos moduladores incluyen, aunque no quedan limitados a los mismos, agonistas, agonistas parciales, antagonistas, y antagonistas parciales.

El término "agonista" en el contexto de los compuestos descritos conforme a la invención se refiere a un compuesto que, cuando se une al receptor de glucocorticoides, mejora o aumenta la función del receptor de glucocorticoides. Como tales, los agonistas incluyen agonistas parciales y agonistas totales.

El término "agonista total" en el contexto de describir los compuestos conforme a la invención se refiere a un compuesto que obtiene la respuesta estimuladora máxima del receptor de glucocorticoides, incluso cuando están presentes receptores de glucocorticoides libres (no ocupados).

El término "agonista parcial" en el contexto de describir los compuestos conforme a la invención se refiere a un compuesto que no puede obtener la respuesta estimuladora máxima del receptor de glucocorticoides, incluso en concentraciones suficientes para saturar los receptores de glucocorticoides presentes.

El término "antagonista" en el contexto de describir los compuestos conforme a la invención se refiere a un compuesto que inhibe directa o indirectamente la función del receptor de glucocorticoides. Como tales, los antagonistas incluyen antagonistas parciales y antagonistas totales.

El término "antagonista total" en el contexto de describir los compuestos conforme a la invención se refiere a un compuesto que obtiene la respuesta inhibidora máxima del receptor de glucocorticoides, incluso cuando están presentes receptores de glucocorticoides libres (no ocupados).

El término "antagonista parcial" en el contexto de describir los compuestos conforme a la invención se refiere a un compuesto que no puede obtener la respuesta inhibidora máxima del receptor de glucocorticoides, incluso en concentraciones suficientes para saturar los receptores de glucocorticoides presentes

Los términos "tratar" o "tratamiento" se refieren al tratamiento de un estado de

enfermedad en un paciente, e incluyen:

(i) prevenir la aparición del estado de enfermedad en un paciente, en particular, cuando dicho paciente está predispuesto genéticamente o por cualquier otro motivo al estado de enfermedad aunque todavía no se le haya diagnosticado;

(ii) inhibir o mejorar el estado de enfermedad en un paciente, es decir, detener o ralentizar su desarrollo; o

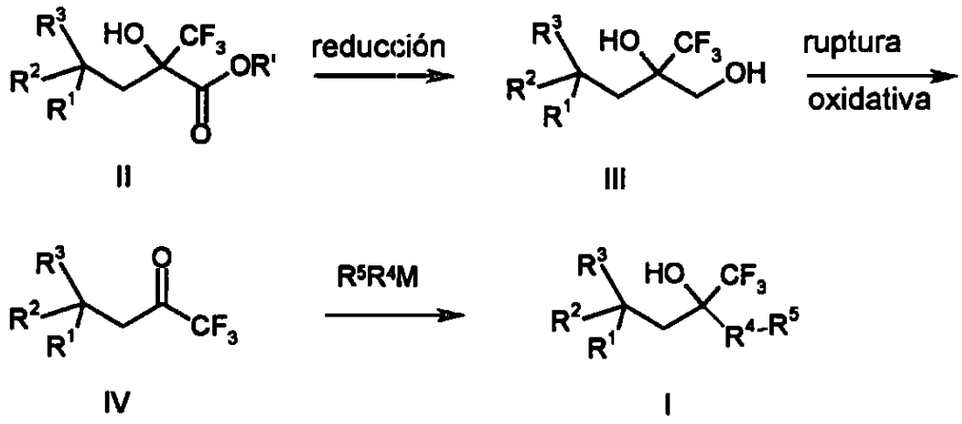
(iii) aliviar el estado de enfermedad en un paciente, es decir, provocar la regresión o curación del estado de enfermedad.

Procedimientos generales de síntesis para preparar compuestos de Fórmula (IA) y Fórmula (IB)

La invención también proporciona procedimientos para preparar compuestos de Fórmula (IA) y Fórmula (IB). En todos los esquemas, a no ser que se indique de otro modo, R^1 a R^5 en las fórmulas siguientes tendrán el significado de R^1 a R^5 en la Fórmula (IA) de la invención descrita antes en la presente memoria; y cuando sea apropiado, R^1 a R^6 en las fórmulas siguientes tendrán el significado usado en la Fórmula (IB) de la invención descrita antes en la presente memoria. Los intermedios usados en la preparación de compuestos de la invención están disponibles de forma comercial o se preparan fácilmente por procedimientos conocidos por los expertos en la técnica.

Las condiciones óptimas de reacción y los tiempos de reacción pueden variar dependiendo de los reaccionantes particulares usados. A no ser que se indique de otro modo, disolventes, temperaturas, presiones y otras condiciones específicas de la reacción se pueden seleccionar fácilmente por un experto en la técnica. En la sección de Ejemplos experimentales se proporcionan procedimientos específicos. De forma típica, el progreso de la reacción se puede controlar por cromatografía en capa fina (TLC), si se desea, y los intermedios y productos se pueden purificar por cromatografía sobre gel de sílice y/o recristalización.

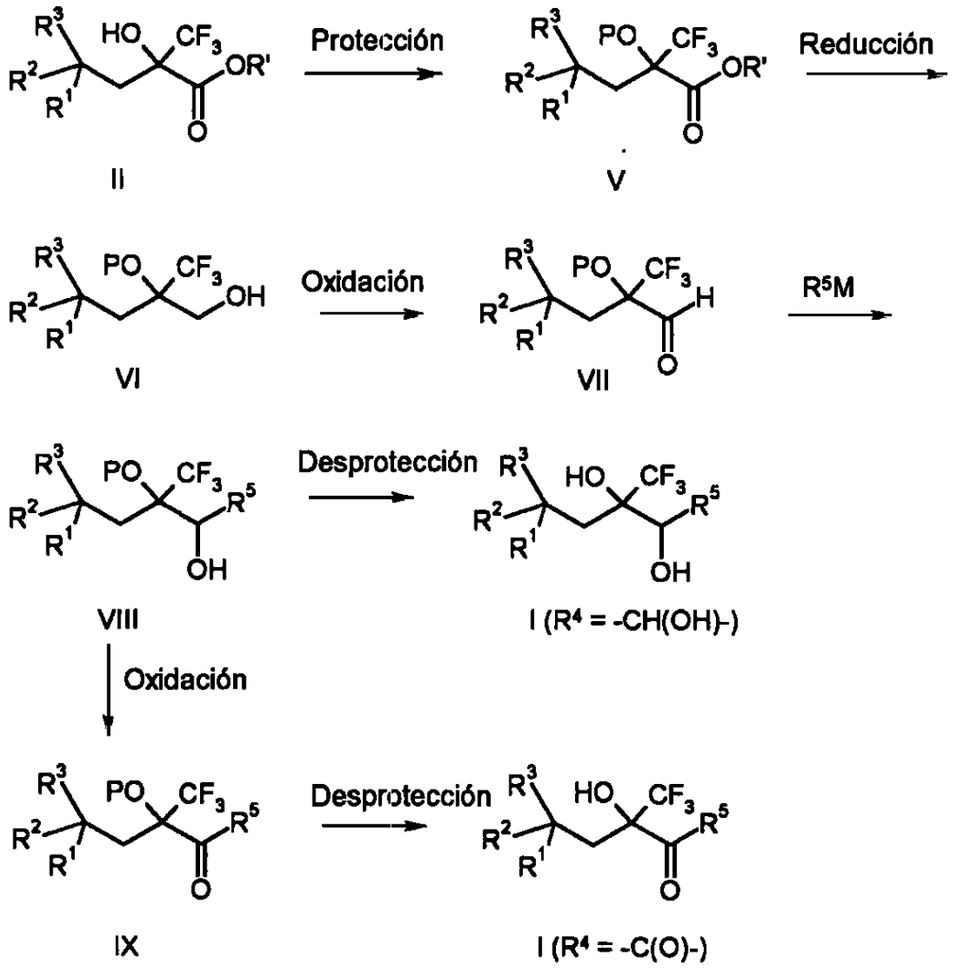
Los compuestos de Fórmula (I) se puede preparar por el procedimiento representado en el Esquema I.



Esquema I

Como se ilustra en el Esquema I, se reduce un intermedio éster de Fórmula (II) en el que R' es Me o Et, con un agente reductor adecuado, como hidruro de litio y aluminio, en un disolvente adecuado, como THF o éter dietílico, produciendo el 1,2-diol de Fórmula (III). La ruptura oxidativa de los 1,2-dioles es bien conocida en la técnica y se puede conseguir con ácido peryódico o tetraacetato de plomo, por ejemplo, en un disolvente adecuado como metanol, proporcionando la cetona (IV). La reacción de la cetona (IV) con un reactivo orgamometálico adecuado R^5R^4M, tal como un reactivo de Grignard (M es MgBr o MgCl) o un reactivo de organolitio (M es Li) en un disolvente adecuado como THF o éter dietílico proporciona el compuesto deseado de Fórmula (I). Dichos reactivos de organolitio y haluros de alquilmagnesio o reactivos de Grignard son bien conocidos en la técnica, por ejemplo, los reactivos de Grignard se preparan fácilmente haciendo reaccionar el haluro de alquilo correspondiente con magnesio metálico en un disolvente adecuado, como éter o THF en condiciones anhidras.

El Esquema II representa otra técnica que se puede usar para obtener compuestos de Fórmula (I).

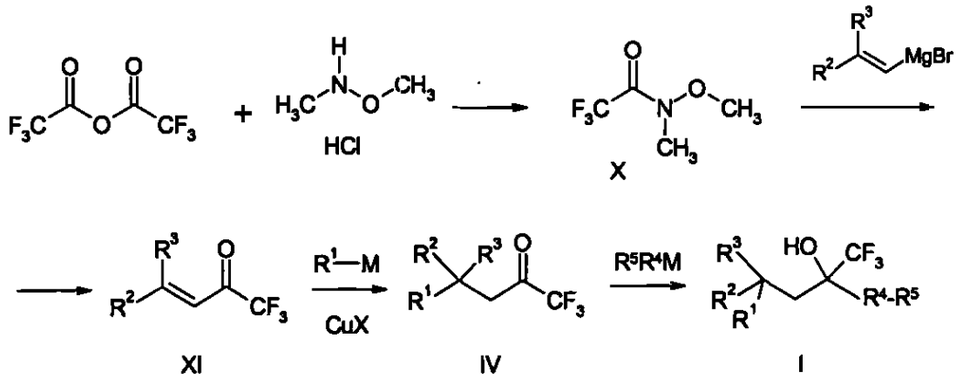


Esquema II

En el Esquema II, se protege la función hidroxilo en el intermedio (II) proporcionando un éster (V). Grupos protectores de hidroxilo son bien conocidos en la técnica, un ejemplo de un grupo protector de hidroxilo es un éter metoximetílico. La reducción del éster (V) con un agente reductor adecuado tal como hidruro de litio y aluminio proporciona el alcohol (VI). La oxidación del alcohol (VI) con un agente oxidante como clorocromato de piridinio (PCC) proporciona el aldehído (VII). El tratamiento del aldehído (VII) con un reactivo organometálico adecuado R^5M en el que M es Li o MgX, y X es Cl, Br o I, es decir, un reactivo de organolitio o reactivo de Grignard o haluro de alquilmagnesio que tiene R^5, proporciona el alcohol (VIII). La desprotección por procedimientos convencionales que dependerán del grupo protector usado, da el compuesto deseado de Fórmula (I) en la que R^4 es -CH(OH)-. La oxidación del alcohol (VIII) a (IX) con un agente oxidante tal como PCC o 1,1,1-triacetoxi-1,1-dihidro-1,2-

benzoyodoxol-3(1*H*)-ona, seguida por desprotección proporciona el compuesto deseado de Fórmula (I) en la que R^4 es -C(O)-.

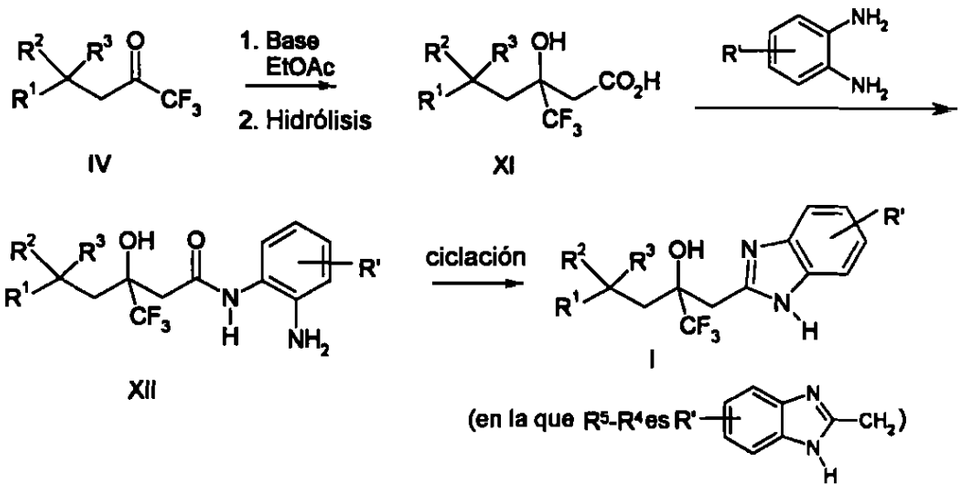
Los compuestos de Fórmula (I) también se pueden preparar por el procedimiento representado en el Esquema III.



Esquema III

En esta técnica, se acoplan anhídrido trifluoroacético e hidrocloruro de *N,O*-dimetilhidroxilamina en condiciones básicas proporcionando trifluoroacetamida (X) (amida de Weinreb). La amida de Weinreb (X) se hace reaccionar con un bromuro de vinil-magnesio que tiene R^2 y R^3 proporcionando el intermedio (XI) de trifluorometilenona. El intermedio (XI) de trifluorometilenona se trata con un reactivo de organocobre derivado de un reactivo de Grignard u organolitio tratando con una sal de cobre, proporcionando el producto de adición 1,4 (IV). Este intermedio de trifluorocetona (IV) se hace reaccionar con un reactivo organometálico R^4R^5M (como se describe en el Esquema I) proporcionando el compuesto deseado de Fórmula (I).

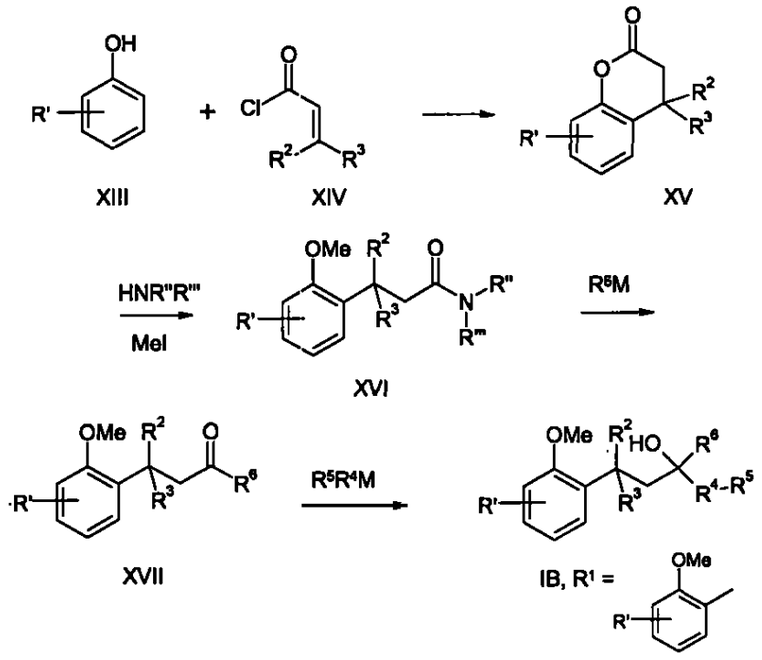
Los compuestos de Fórmula (I) en la que R^4-R^5 es un grupo bencimidazol-2-ilmetilo opcionalmente sustituido también se pueden preparar por el procedimiento representado en el Esquema IV.



Esquema IV

Como se ilustra en el Esquema IV, se hace reaccionar trifluorometilcetona (IV) con acetato de etilo en presencia de una base fuerte como diisopropilamida de litio (LDA) en un disolvente adecuado como THF. El éster intermedio se hidroliza, por ejemplo, por tratamiento con base acuosa, proporcionando el intermedio de ácido carboxílico (XII). Este intermedio de ácido carboxílico (XII) se acopla a continuación con una *o*-fenilendiamina opcionalmente sustituida en condiciones convencionales de acoplamiento conocidas en la técnica, por ejemplo, por tratamiento con 1-(3-dimetilaminopropil)-3-etilcarbodiimida (EDC) en presencia de 1-hidroxibenzotriazol en un disolvente adecuado como DMF, proporcionando el compuesto (XIII). El cierre del anillo por procedimientos conocidos en la técnica, por ejemplo, cierre del anillo catalizado por ácido mediante tratamiento con ácido polifosfórico, proporciona el compuesto deseado de Fórmula (I).

Los compuestos de Fórmula (IB) se pueden preparar por el procedimiento ilustrado en el Esquema V

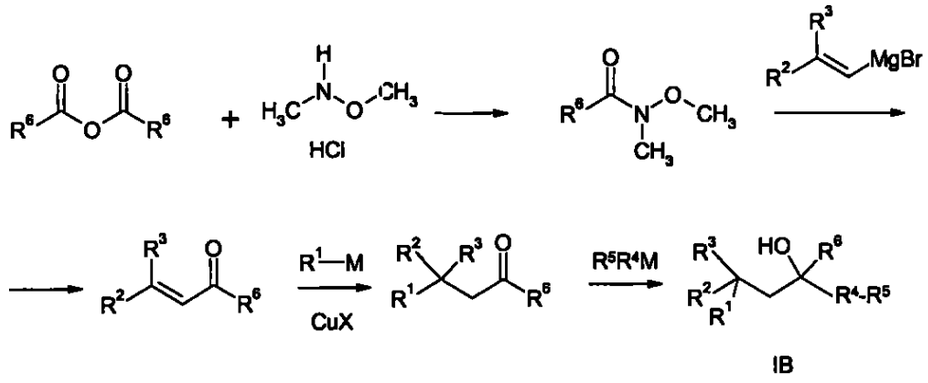


Esquema V

En el Esquema V, se hace reaccionar el fenol sustituido (XIV) con un cloruro de acriloilo que tiene R^2 y R^3 (XV) en presencia de una base adecuada, como trietilamina, proporcionando un éster intermedio que se cicla por tratamiento con un ácido de Lewis, como tricloruro de aluminio, en un disolvente adecuado, como disulfuro de carbono, proporcionando la lactona (XVI). La lactona (XVI) se trata con una amina adecuada HNR''R''', tal como morfolina, de modo que en la amida resultante (XVII), -NR''R''' funcionará como un grupo lábil en la siguiente reacción. El fenol intermedio que se forma se protege, por ejemplo, por reacción con yoduro de metilo en presencia de una base adecuada como hidróxido potásico formando el fenol protegido (XVII), en este caso con un grupo metoxi. La amida se hace reaccionar entonces con un reactivo organometálico (R^6M), tal como un reactivo de Grignard (M es MgBr o MgCl) o un reactivo de organolitio (M es Li) en un disolvente adecuado, como THF o éter dietílico, proporcionando la cetona (XVIII). La reacción de la cetona (XVIII) con R^5R^4M como se describe en la última etapa del Esquema I proporciona el compuesto deseado de Fórmula (IB) en la que R^1 es un grupo metoxifenilo opcionalmente sustituido.

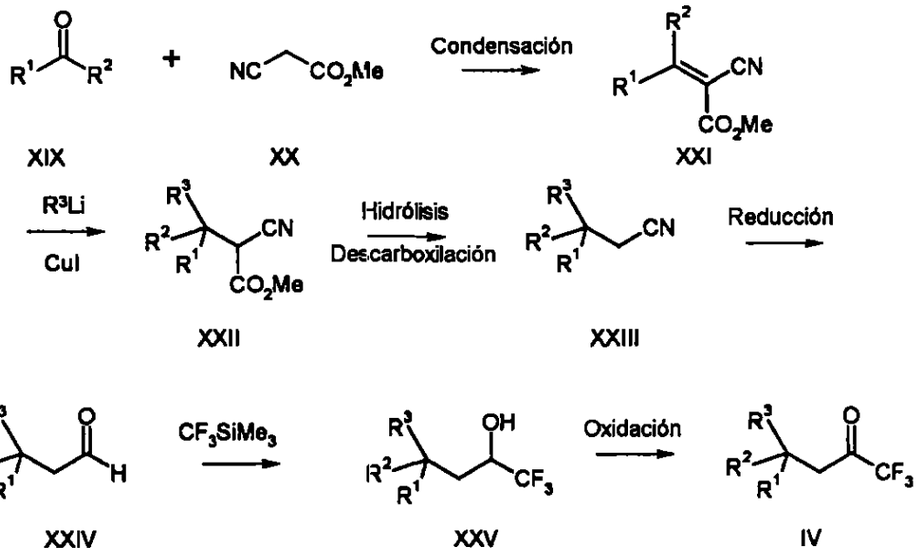
En un procedimiento más general, adecuado para una diversidad de R^1, se puede usar un método análogo al descrito en el Esquema III. Como se ilustra en el Esquema VI, usando una amida de Weinreb que tiene R^6 se puede emplear el procedimiento descrito

en el Esquema III para preparar el compuesto deseado de Fórmula (IB).



Esquema VI

En el Esquema VII se ilustra un procedimiento alternativo para preparar el intermedio (IV), usado en los procedimientos ilustrados en los Esquemas I-IV.



Esquema VII

En el Esquema VII, se hace reaccionar una cetona que tiene R^1 y R^2 (XIX) con un éster de ácido cianoacético, tal como éster metílico (XX) en condiciones de condensación conocidas en la técnica proporcionando la olefina (XXI). La reacción de la olefina (XXI) con R^3Li en presencia de una sal de cobre como CuI proporciona el compuesto (XXII). La hidrólisis y descarboxilación del compuesto (XXII) produce el nitrilo (XXIII). La reducción del nitrilo (XXIII), por ejemplo, por tratamiento con hidruro de diisobutilaluminio (DIBAL) proporciona el aldehído (XXIV). El tratamiento del

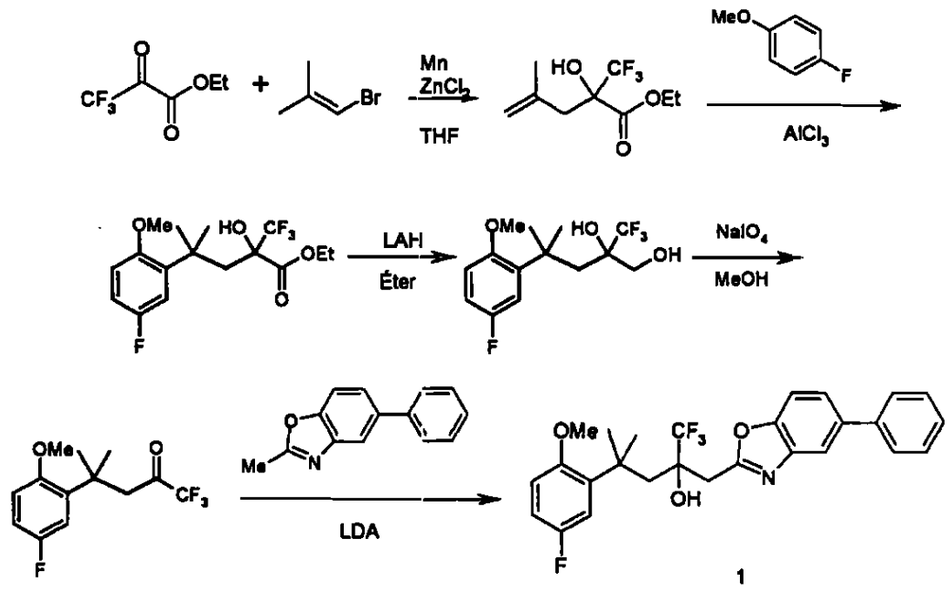
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aldehído (XXIV) con trimetil(trifluorometil)silano en presencia de una sal de amonio como fluoruro de tetrabutilamonio proporciona el alcohol (XXV). La oxidación del alcohol (XXV) por procedimientos conocidos en la técnica, tal como por tratamiento con peryodinano de Dess-Martin, proporciona el compuesto (IV).

Con el fin de que pueda comprenderse mejor esta invención, se presentan los siguientes ejemplos. Estos ejemplos tienen el objeto de ser ilustraciones de realizaciones de esta invención, y no se considerará que limitan el alcance de la invención en modo alguno, como se reconocerá por un experto en la técnica, los reaccionantes o condiciones particulares se podrán modificar según sea necesario para los compuestos particulares. Los materiales de partida usados están disponibles de forma comercial o se preparan fácilmente por los expertos en la técnica a partir de materiales disponibles comercialmente.

Ejemplos experimentales

Ejemplo 1: Síntesis de 1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(5-fenilbenzoxazol-2-ilmetil)pentan-2-ol



1

Se añadieron 200 µl (2 mmol) de 1-bromo-2-metilpropeno a una mezcla de 8,5 g (49,9 mmol) de trifluorometilpiruvato de etilo, 6,6 g (120 mmol) de manganeso y 0,65 g (4,8 mmol) de cloruro de cinc en 40 ml de THF calentado hasta reflujo. Después de 30 minutos, se añadieron, gota a gota durante un período de 1 hora 9,13 ml (90,5 mmol) de 1-bromo-2-metilpropeno en 30 ml de THF. La mezcla se llevó a reflujo durante 1 hora

después de la adición y a continuación se enfrió hasta 0°C y se diluyó con 150 ml de cloruro de amonio acuoso saturado y 100 ml de EtOAc. La fase orgánica se separó y se extrajo la fase acuosa con tres porciones de 100 ml de EtOAc. Las fases orgánicas reunidas se lavaron con dos porciones de 50 ml de cloruro amónico acuoso saturado, seguido por dos porciones de 50 ml de salmuera, se secaron sobre sulfato magnésico ($MgSO_4$), se filtraron y se concentraron a vacío. El residuo bruto se purificó por cromatografía sobre gel de sílice eluyendo con EtOAc-hexanos (5:95) proporcionando 5,9 g (52%) de éster etílico del ácido 2-hidroxi-4-metil-2-trifluorometilpent-4-enoico.

Se añadieron en varias porciones 5,2 g (39,4 mmol) de cloruro de aluminio a una mezcla de 5,9 g (26,1 mmol) del anterior éster etílico del ácido 2-hidroxi-4-metil-2-trifluorometilpent-4-enoico en 30 ml de 4-fluoroanisol. La mezcla se hizo exotérmica y viró a color negro con la primera adición y se enfrió con un baño de hielo-agua. La mezcla se agitó durante 3 días y luego se vertió en 200 ml de HCl acuoso 1N enfriado en hielo y se extrajo con tres porciones de 150 ml de EtOAc. Las capas orgánicas reunidas se lavaron con 50 ml de ácido clorhídrico acuoso 1N, tres porciones de 50 ml de salmuera, se secaron sobre sulfato magnésico, se filtraron y se concentraron a vacío. El residuo bruto se purificó por cromatografía en columna sobre gel de sílice eluyendo con EtOAc-hexanos (1:9, luego 2:8, luego 3:7, luego 4:6) proporcionando 6,6 g (71%) del éster etílico del ácido 4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentanoico.

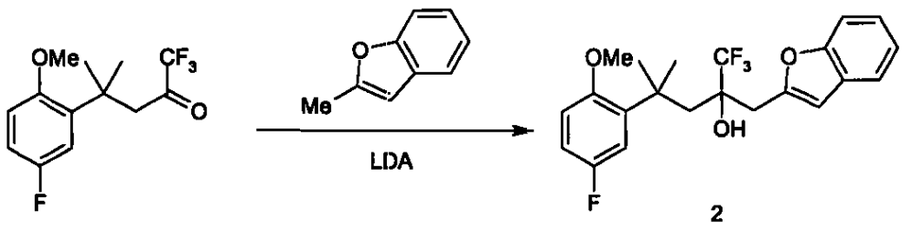
Se añadieron 2,4 g (61,5 mmol) de hidruro de litio y aluminio en porciones a una solución enfriada (baño de hielo-agua) de 6 g (17,0 mmol) del anterior éster etílico del ácido 4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentanoico en 60 ml de THF seco. Después de la adición, se retiró el baño de enfriamiento y se agitó la mezcla a temperatura ambiente durante toda la noche. La mezcla se calentó a continuación a reflujo durante 3 horas y luego se inactivó cuidadosamente mediante la adición lenta de 100 ml de THF que contenía 2 ml de agua. Se añadió cuidadosamente agua adicional hasta un total de 15 ml y la mezcla resultante se agitó durante 2 horas. El agua en exceso se secó sobre sulfato de magnesio y se añadieron 300 ml de EtOAc. Después de 1 hora, se filtró la mezcla a través de tierra de diatomeas y se concentró a vacío proporcionando 4,9 g (92%) de 4-(5-fluoro-2-metoxifenil)-4-metil-2-trifluorometilpentano-1,2-diol como un aceite.

Se añadieron 10 g (45,9 mmol) de peryodato sódico a una solución de 4,9 g (15,8 mmol) del anterior 4-(5-fluoro-2-metoxifenil)-4-metil-2-trifluorometilpentano-1,2-diol

en 100 ml de MeOH. La mezcla se agitó durante 4 horas y luego se diluyó con 100 ml de éter y 100 ml de hexanos, se filtró a través de tierra de diatomeas y se concentró a vacío. El residuo bruto se disolvió en hexanos y se hizo pasar a través de un lecho de gel de sílice eluyendo primero con hexanos y luego con EtOAc-hexanos (2:98, luego 4:96) proporcionando 3,85 g (87%) de 1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ona como un aceite transparente.

Se añadió *n*-butil litio (0,246 ml, 1,6 M en hexanos) a una solución de diisopropil amina (0,055 ml, 0,45 mmol) en THF anhidro (5 ml) a 0°C. La mezcla de reacción se enfrió hasta -78°C y se agitó durante 15 minutos. Se añadió a esta mezcla, gota a gota, 2-metil-5-fenil benzoxazol (75 mg, 0,4 mmol) disuelto en THF anhidro (2 ml). Después de la adición, la mezcla de reacción se agitó durante 15 a 30 minutos. Se añadió 1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ona (100 mg, 0,4 mmol) en forma de una solución en THF anhidro (2 ml), se retiró el baño de enfriamiento y se agitó la reacción a temperatura ambiente durante 12 horas. Se evaporó el THF a presión reducida. Se añadió agua (2 ml) al residuo y la mezcla se extrajo con tres porciones de 5 ml de EtOAc. El extracto se secó sobre sulfato de magnesio. Después de evaporar, se sometió el residuo a cromatografía sobre una columna de gel de sílice proporcionando 150 mg del compuesto del epígrafe como cristales blancos, p.f. 103°C-104°C.

Ejemplo 2: Síntesis de 2-benzoxazol-2-ilmetil-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol



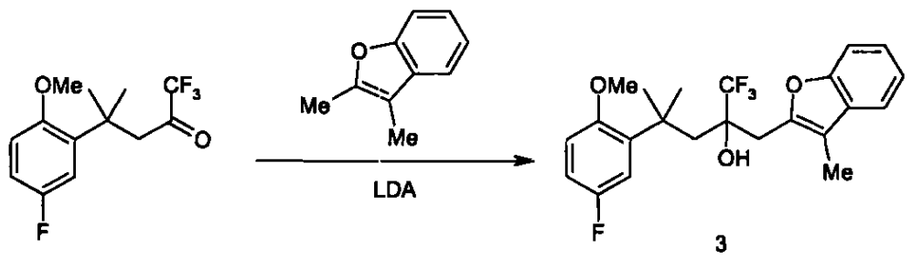
2

Se añadió *n*-butil litio (0,246 ml, 1,6 M en hexanos) a una solución de diisopropil amina (0,055 ml, 0,45 mmol) en THF anhidro (5 ml) a 0°C. La mezcla de reacción se enfrió hasta -78°C y se agitó durante 15 minutos. Se añadió, gota a gota a esta mezcla una solución de 2-metilbenzofurano (48 mg, 0,4 mmol) en 2 ml de THF anhidro. Después de la adición, la mezcla de reacción se agitó durante 15 a 30 minutos. Se añadió como una solución en THF anhidro (2 ml) 1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ona (100 mg, 0,4 mmol) (Ejemplo 1) en una porción, se retiró el baño de enfriamiento y la reacción se agitó a temperatura ambiente durante 12 horas. Se evaporó el THF a presión reducida. Se añadió agua (2 ml) al residuo y la mezcla se extrajo con

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tres porciones de 5 ml de EtOAc. El extracto se secó sobre sulfato de magnesio. Después de evaporar, el residuo se sometió a cromatografía sobre una columna de gel de sílice, proporcionando 86 mg del compuesto del epígrafe como un aceite.

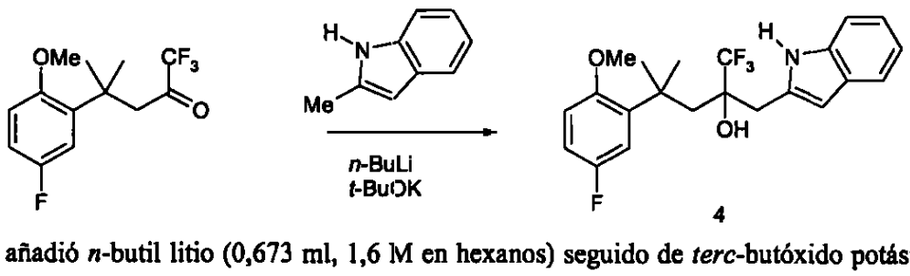
Ejemplo 3: Síntesis de 1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(3-metilbenzofuran-2-ilmetil)pentan-2-ol



3

Se añadió *n*-butil litio (0,246 ml, 1,6 M en hexanos) a una solución de diisopropil amina (0,055 ml, 0,45 mmol) en THF anhidro (5 ml) a 0°C. La mezcla de reacción se enfrió hasta -78°C y se agitó durante 15 minutos. Se añadió, gota a gota a esta mezcla, una solución de 2,3-dimetilbenzofurano (48 mg, 0,4 mmol) en 2 ml de THF anhidro. Después de la adición, la mezcla de reacción se agitó durante 15 a 30 minutos. Se añadió como una solución en THF anhidro (2 ml) 1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ona (100 mg, 0,4 mmol) (Ejemplo 1) en una porción, se retiró el baño de enfriamiento y la reacción se agitó a temperatura ambiente durante 12 horas. Se evaporó el THF a presión reducida. Se añadió agua (2 ml) al residuo y la mezcla se extrajo con tres porciones de 5 ml de EtOAc. El extracto se secó sobre sulfato de magnesio. Después de evaporar, el residuo se sometió a cromatografía sobre una columna de gel de sílice proporcionando 80 mg del compuesto del epígrafe como un aceite.

Ejemplo 4: Síntesis de 1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol



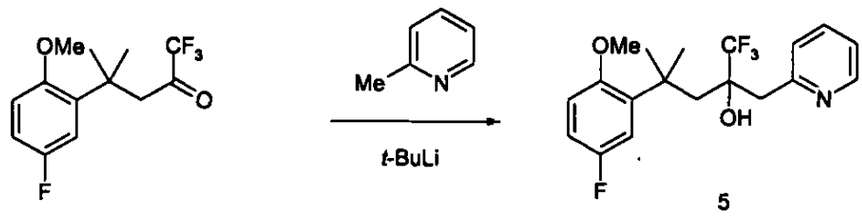
4

Se añadió *n*-butil litio (0,673 ml, 1,6 M en hexanos) seguido de *terc*-butóxido potásico (81 mg, 0,718 mmol) a una solución de 2-metil indol (47 mg, 0,359 mmol) en éter

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dietílico anhidro (5 ml) a temperatura ambiente. En 5 a 10 minutos, la mezcla de reacción viró a color naranja brillante. Se añadió gota a gota como una solución en éter dietílico anhidro (2 ml) 1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ona (100 mg, 0,4 mmol) (Ejemplo 1). La reacción se inactivó con agua después de 1 hora, se extrajo con tres porciones de 5 ml de EtOAc, se secó sobre sulfato de magnesio y se concentró a presión reducida. El residuo se purificó por cromatografía en columna sobre gel de sílice proporcionando 45 mg del compuesto del epígrafe como un aceite.

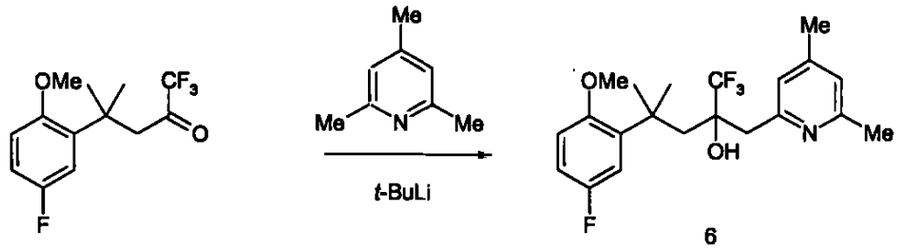
Ejemplo 5: Síntesis de 1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-2-(piridin-2-ilmetil)-4-metilpentan-2-ol



5

Se añadió, gota a gota *terc*-butil litio (1,7 M en pentano, 0,5 ml) a una solución de 2-metilpiridina (0,050 g) en THF (0,5 ml) enfriado hasta -70°C en argon. La mezcla se agitó a -70°C durante 10 minutos y se añadió durante 1 minuto 1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ona (0,080 g) (Ejemplo 1) en THF (0,5 ml). La mezcla de reacción se agitó durante 5 minutos y luego se inactivó con MeOH. La mezcla de reacción se concentró a vacío y el residuo se fraccionó directamente por cromatografía en capa de preparación sobre gel de sílice (cloruro de metileno-hexanos) (1:1), proporcionando 57 mg del compuesto del epígrafe, p.f. 94°C-96°C.

Ejemplo 6: Síntesis de 1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-2-(4,6-dimetilpiridin-2-ilmetil)-4-metilpentan-2-ol

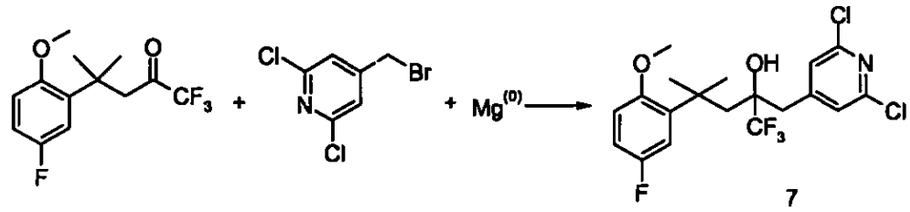


6

Se añadió *terc*-butil litio (1,7 M en pentano, 0,5 ml) a una solución de 2,4,6-trimetilpiridina (0,12 g) en THF (0,5 ml) enfriada hasta -70°C en argon. La mezcla se agitó a -70°C durante 15 minutos y se añadió 1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ona (0,10 g) (Ejemplo 1) en THF (0,5 ml). La mezcla de reacción se

agitó durante 20 minutos y luego se inactivó con ácido acético. La mezcla se diluyó con EtOAc, se lavó con agua, se secó, se filtró y se concentró a vacío. El fraccionamiento por cromatografía en capa de preparación sobre gel de sílice (cloruro de metileno-hexanos) seguido por cristalización proporcionó 43 mg del compuesto del epígrafe, p.f. 95°C-98°C.

Ejemplo 7: Síntesis de 2-(2,6-dicloropiridin-4-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol

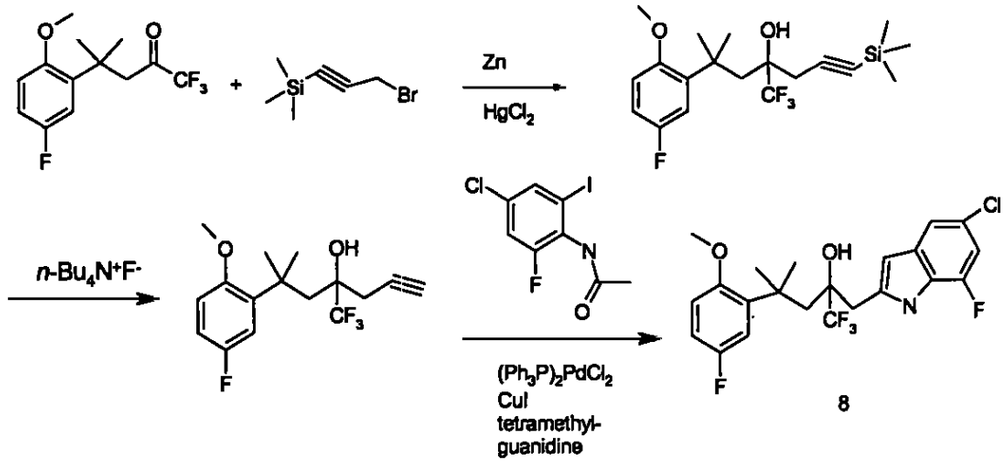


7

Se añadieron 73 mg (3,0 mmol) de polvo de magnesio, un par de cristales de I_2 y 5 ml de éter dietílico seco a un matraz de fondo redondo seco de 100 ml y la mezcla se dejó agitar en argon. Se añadió gota a gota a través de un embudo de adición 4-bromometil-2,6-dicloropiridina (723 mg; 3,0 mmol) en 10 ml de éter dietílico y la mezcla resultante se calentó hasta reflujo durante 1 hora. Se añadió cuidadosamente gota a gota a través de un embudo de adición 1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ona (278 mg, 1,0 mmol) (Ejemplo 1) en éter dietílico (5 ml) y la mezcla se dejó agitar hasta temperatura de reflujo durante 4 horas y luego durante toda la noche (16 horas) a temperatura ambiente. La reacción se inactivó con la adición de 3 ml de solución acuosa de NH_4Cl y la mezcla resultante se extrajo con tres porciones de 30 ml de EtOAc, se lavó con agua (10 ml) y salmuera (10 ml) y la fase orgánica se secó sobre Na_2SO_4, se filtró y se concentró a vacío. El residuo se purificó por cromatografía ultrarrápida sobre gel de sílice usando un gradiente de EtOAc-hexanos. Las fracciones de productos reunidas se concentraron a vacío proporcionando el producto deseado que se purificó luego por HPLC de preparación usando un gradiente de 80%-100% (CH_3CN-agua) en 15 minutos y un caudal de 20 ml/min, proporcionando 76 mg del compuesto del epígrafe (17,2% de rendimiento) como un líquido amarillento.

Ejemplo 8: Síntesis de 2-(5-cloro-7-fluoro-1*H*-indol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol

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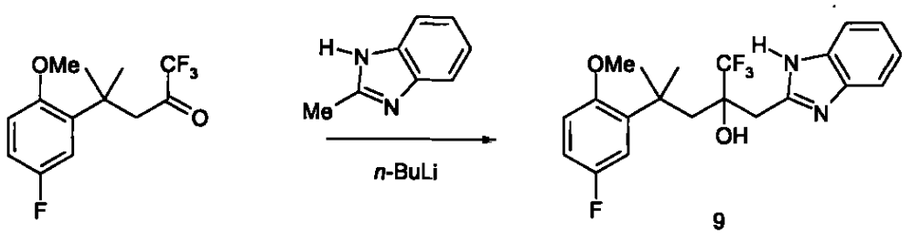
Se enfrió sobre hielo una suspensión agitada de polvo de cinc (0,656 g) y cloruro mercúrico (25 mg) en 5 ml de THF anhidro. Se añadió una solución de bromuro de trimetilsilil-propargilo (0,96 g, 5 mmol) en THF anhidro (1 ml), se retiró el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente durante 20 horas. Se añadió una solución de 1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ona (0,2 g, 0,72 mmol) (Ejemplo 1) en THF anhidro (1 ml) a una solución del reaccionante de organocinc resultante y la mezcla de reacción se agitó a temperatura ambiente durante 4 horas. La TLC (hexanos-EtOAc (95:5)) indicó el consumo del material de partida con una mancha más polar única. La mezcla de reacción se inactivó con una solución saturada de cloruro amónico. La mezcla resultante se extrajo con tres porciones de 30 ml de diclorometano, los extractos reunidos se lavaron con dos porciones de 20 ml de agua, se secaron sobre sulfato sódico anhidro y se concentraron a vacío. El producto bruto se purificó por cromatografía en columna sobre gel de sílice eluyendo con hexanos-EtOAc (95:5) proporcionando el alcohol intermedio deseado como un aceite incoloro.

Se añadieron 0,5 ml de una solución 1M de fluoruro de tetrabutilamonio en THF a una solución agitada del alcohol anterior (200 mg, 0,51 mmol) en THF anhidro (2 ml) enfriado en hielo. Después de 30 minutos, la TLC en hexanos-EtOAc (95:5) indicó el consumo del material de partida. La mezcla de reacción se inactivó con solución saturada de cloruro amónico (5 ml), se extrajo con éter (100 ml), se lavó con dos porciones de 25 ml de agua, se secó sobre sulfato sódico anhidro y se concentró a vacío proporcionando el intermedio de acetileno terminal deseado (160 mg, 98%).

Se agitó y se calentó en un baño de aceite mantenido a 80°C durante 20 horas una

mezcla del intermedio de acetileno anterior (85 mg, 0,27 mmol), 4-cloro-2-fluoro-6-yodoacetanilida (90 mg, 0,29 mmol), catalizador de cloruro de bis(trifenilfosfina)paladio(II) (20 mg, 0,028 mmol), yoduro de cobre (I) (8 mg, 0,042 mmol) y tetrametilguanidina (0,2 ml) en dioxano anhidro (0,5 ml). Después de enfriar hasta temperatura ambiente, la mezcla de reacción se diluyó con diclorometano (25 ml) y se filtró a través de tierra de diatomeas, que se aclararon seguidamente con diclorometano. El filtrado y las aguas de lavado se recogieron, se lavaron con tres porciones de 20 ml de H_2SO_4 1N, tres porciones de 20 ml de agua, se secaron sobre sulfato sódico anhidro y se concentraron a vacío proporcionando un aceite pardusco. El producto bruto se purificó por TLC de preparación eluyendo con hexanos-EtOAc (90:10). Se recogió la banda correspondiente a R_f 0,26, proporcionando el compuesto como un aceite.

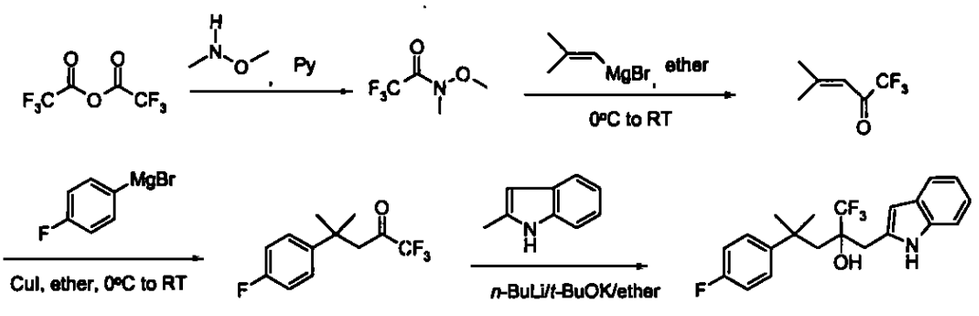
Ejemplo 9: Síntesis de 2-(1*H*-bencimidazol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol



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Se añadió lentamente *n*-butil litio (1,6M en pentanos, 3 ml, 4,8 mmol) a una solución de 2-metilbencimidazol (300 mg, 2,3 mmol) en 20 ml de THF anhidro a -30°C. La mezcla heterogénea de color rojo resultante se agitó durante 2 horas a esta temperatura y luego se añadió gota a gota una solución de 1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ona (700 mg, 2,55 mmol) (véase el Ejemplo 1) en THF anhidro (1 ml).Se dejó que la temperatura de reacción se enfriara lentamente durante un período de 2 horas, momento en el que se trató la reacción con solución saturada de NH_4Cl. La mezcla resultante se extrajo con éter dietílico. Los extractos orgánicos reunidos se secaron sobre sulfato de magnesio, se filtraron y se concentraron a vacío proporcionando un aceite que se purificó por cromatografía sobre gel de sílice proporcionando 200 mg de 2-metilbencimidazol no modificado y 60 mg del compuesto del epígrafe como un sólido blanco, p.f. 80°C-82°C.

Ejemplo 10: Síntesis de 2-(1*H*-indol-2-ilmetil)-1,1,1-trifluoro-4-(4-fluorofenil)-4-metilpentan-2-ol



10

Se añadieron 21,7 ml de anhídrido trifluoroacético, gota a gota a 0°C, a una mezcla de 15,8 g de hidrocloruro de *N,O*-dimetilhidroxilamina en 400 ml de CH_2Cl_2. Se añadió entonces piridina (37 ml) a la mezcla anterior gota a gota a 0°C. La mezcla resultante se dejó agitando a 0°C durante 30 minutos y luego se inactivó con agua. La capa orgánica se lavó con agua, HCl acuoso 1N, agua y salmuera, se secó sobre sulfato magnésico, se filtró y se concentró a vacío. El residuo se bombeó a vacío durante 5 minutos proporcionando 2,2,2-trifluoro-*N*-metoxi-*N*-metilacetamida como un aceite incoloro.

Se enfrió hasta 0°C una mezcla de 3 g de 2,2,2-trifluoro-*N*-metoxi-*N*-metilacetamida y 30 ml de éter anhidro y se trató con 42 ml de una solución 0,5M de bromuro de 2-metil propenilmagnesio en THF. La reacción se agitó a 0°C durante 0,5 minutos y luego se calentó hasta temperatura ambiente y se agitó durante toda la noche. La reacción se inactivó con NH_4Cl acuoso saturado y se extrajo con éter tres veces. Las capas orgánicas se reunieron y se lavaron con agua y salmuera, se secaron sobre sulfato de magnesio y se filtraron. La solución resultante en éter/THF de 1,1,1-trifluoro-4-metilpent-3-en-2-ona se usó para la siguiente reacción sin purificación adicional.

Se añadieron 3,8 g de yoduro de cobre (I) y 10 ml de una solución 2M en éter de bromuro de 4-fluorofenilmagnesio a 0°C a una solución 2M en éter /THF de 1,1,1-trifluoro-4-metilpent-3-en-2-ona. La mezcla se calentó hasta temperatura ambiente y se agitó durante 2 horas. La reacción se inactivó con NH_4Cl acuoso saturado y se extrajo tres veces con EtOAc. Las capas orgánicas reunidas se lavaron con agua, salmuera, se secaron sobre sulfato de magnesio, se filtraron y se concentraron a vacío. El residuo se purificó por cromatografía ultrarrápida proporcionando 460 mg de 1,1,1-trifluoro-4-(4-fluorofenil)-4-metilpentan-2-ona.

Se añadieron 3 equivalentes de *n*-butil litio, seguidos de 90 mg de *terc*-butóxido potásico (*t*-BuOK) (sólido) a temperatura ambiente a una solución en éter dietílico de 53

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mg de 2-metilindol. La mezcla se dejó agitando durante 30 minutos. Se añadió entonces a la mezcla anterior 1,1,1-trifluoro-4-(4-fluorofenil)-4-metilpentan-2-ona (100 mg) en éter dietílico. La reacción se agitó a temperatura ambiente durante una hora. La reacción se inactivó con cloruro amónico acuoso saturado y se extrajo tres veces con EtOAc. Las capas orgánicas reunidas se lavaron con agua, salmuera, se secaron sobre sulfato de magnesio, se filtraron y se concentraron a vacío. El residuo se purificó por cromatografía en columna proporcionando 40 mg del compuesto del epígrafe como una espuma. La resolución de los enantiómeros (+) y (-) se llevó a cabo por HPLC quiral en una columna CHIRALCEL® OD™, eluyendo con isopropanol al 10%-hexanos.

Los siguientes ejemplos se prepararon por procedimientos análogos a los descritos en el Ejemplo 10.

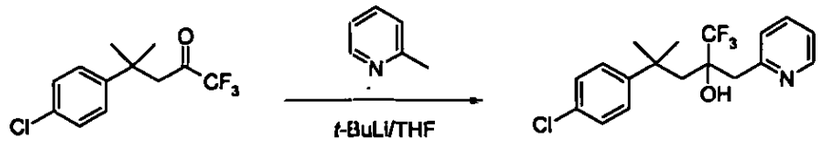
1,1,1-Trifluoro-4-(3-fluorofenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

4-(3,4-Diclorofenil)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol; y

4-(3,4-Difluorofenil)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol.

Ejemplo 11: Síntesis de 4-(4-clorofenil)-1,1,1-trifluoro-4-metil-2-piridin-2-ilmetilpentan-2-ol



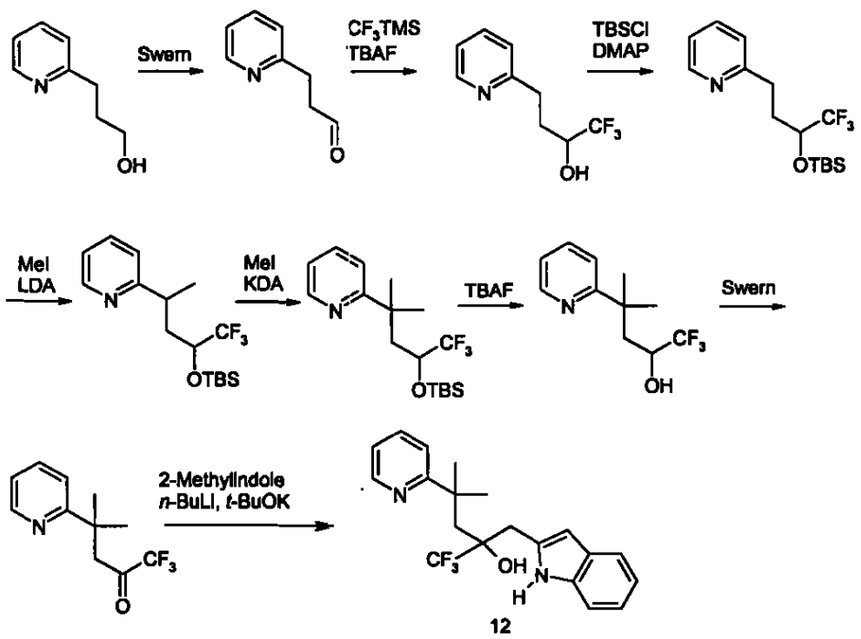
11

Se enfrió hasta -78°C una mezcla de 2-picolina en 1 ml de THF. Se añadió, gota a gota durante 5 minutos *terc*-butil litio (1,7 M en pentanos, 0,2 ml (0,34 mmol)). La mezcla se agitó a -78°C durante 15 minutos y luego se añadió una solución de 40 mg de 4-(4-clorofenil)-1,1,1-trifluoro-4-metilpentan-2-ona en 0,5 ml de THF. Se continuó agitando a -78°C durante 20 minutos. La reacción se inactivó con HCl 0,5N y se extrajo tres veces con EtOAc. Las capas orgánicas se reunieron y se lavaron con agua, salmuera, se secaron sobre sulfato magnésico, se filtraron y se concentraron a vacío. El residuo se purificó por cromatografía en columna proporcionando 9,6 mg del compuesto del epígrafe como un aceite amarillento claro.

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Ejemplo 12: Síntesis de 1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-piridin-2-ilpentan-2-ol

Se diluyó en diclorometano una solución de 4,5 ml (9 mmol, 1,2 eq.) de cloruro de oxalilo (solución 2,0 M en diclorometano). A esta solución se añadió una solución de 1,2 ml (17,5 mmol, 2,4 eq.) de DMSO in 3 ml de diclorometano a -60°C y la mezcla se agitó durante 10 minutos a esta temperatura. A esta mezcla se añadió una solución de 1 g (7,3 mmol) de 4-piridinapropanol en 7 ml de diclorometano a -60°C. La mezcla resultante se agitó a -60°C durante 15 minutos y luego se añadieron 5,0 ml (36,5 mmol, 5,0 eq.) de trietilamina. Se retiró el baño de enfriamiento y se dejó calentar la mezcla de reacción hasta temperatura ambiente y se inactivó con agua. La capa orgánica se separó y la capa acuosa se extrajo tres veces con diclorometano. Las capas orgánicas reunidas se secaron sobre sulfato de magnesio, se filtraron y se concentraron a vacío. El residuo se purificó por cromatografía ultrarrápida proporcionando 3-piridin-2-ilpropionaldehído como un aceite pardo. Rendimiento: 769 mg (78%).



Se trató una solución de 760 mg (5,6 mmol) de 3-piridin-2-ilpropionaldehído en 3 ml de THF con 13,6 ml (6,8 mmol, 1,2 eq.) de trimetil(trifluorometil)silano (solución 0,5 M en THF) y 0,06 ml (0,06 mmol) de fluoruro de tetrabutilamonio (solución 1,0 M en

THF) a 0°C. La mezcla resultante se agitó a 0°C durante 10 minutos y se inactivó con solución 1N de HCl. Después de agitar durante 5 minutos, se ajustó el pH de la mezcla de reacción hasta 9 con solución saturada de $NaHCO_3$, y se extrajo el producto en éter. La capa de éter se lavó con agua y salmuera, se secó sobre sulfato de magnesio y se concentró a vacío. El residuo se purificó por cromatografía ultrarrápida proporcionando 706 mg (61%) de 1,1,1-trifluoro-4-piridin-2-ilbutan-2-ol como un aceite incoloro.

Se trató una solución de 700 mg (3,4 mmol) de 1,1,1-trifluoro-4-piridin-2-ilbutan-2-ol en 10 ml de diclorometano con 616 mg (4,1 mmol, 1,2 eq.) de cloruro de *terc*-butildimetilsililo, 697 mg (10,2 mmol, 3,0 eq.) de imidazol y 415 ng (3,4 mmol) de 4-dimetilaminopiridina a 0°C. La mezcla resultante se dejó calentar hasta temperatura ambiente y se agitó durante 36 horas. A continuación se concentró la mezcla y el residuo se purificó por cromatografía ultrarrápida proporcionando 970 mg (89%) de 2-[3-(*terc*-butildimetilsilaniloxi)-4,4,4-trifluorobutil]piridina como un aceite incoloro.

Se trató con 2,54 ml (3,81 mmol, 1,5 eq.) de LDA (solución 1,5M en ciclohexano) a -75°C una solución de 810 mg (2,54 mmol) de 2-[3-(*terc*-butildimetilsilaniloxi)-4,4,4-trifluorobutil]piridina en 8 ml de THF. Después de agitar a -75°C durante 45 minutos, se añadieron 474 µl (7,61 mmol, 3,0 eq.) de yoduro de metilo a -75°C. La mezcla resultante se agitó a esta temperatura durante 10 minutos y se inactivó con solución saturada de NH_4Cl. El producto se extrajo en éter. La capa de éter se lavó con agua, salmuera, se secó sobre sulfato de magnesio, se filtró y se concentró a vacío proporcionando 750 mg (89%) de 2-[3-(*terc*-butildimetilsilaniloxi)-4,4,4-trifluoro-1-metilbutil]piridina (una mezcla de dos diastereoisómeros) como un aceite pardo.

Se añadieron gota a gota a -75°C 1,55 ml (3,87 mmol, 1,5 eq.) de *n*-butil litio (solución 2,5M en hexanos) a una solución de 3,87 ml (3,87 mmol, 1,5 eq.) de *terc*-butóxido potásico (solución 1,0 M en THF) y 542 µl (3,87 mmol, 1,5 eq.) de diisopropilamina. La mezcla resultante se dejó calentando hasta -50°C durante 15 minutos. A continuación se trató la mezcla de reacción con 860 mg (2,58 mmol) de 2-[3-(*terc*-butildimetilsilaniloxi)-4,4,4-trifluoro-1-metilbutil]piridina a -50°C y la mezcla de reacción se agitó durante 30 minutos a -50°C. La mezcla de reacción se enfrió hasta -75°C y se trató con 482 µl (7,74 mmol) de yoduro de metilo y se agitó durante 1 minuto. La mezcla de reacción se inactivó con solución saturada de NH_4Cl y el producto se extrajo en éter. La capa de éter se lavó con agua y salmuera, se secó sobre sulfato de magnesio, se filtró y se concentró a vacío. El residuo se purificó por cromatografía ultrarrápida proporcionando 555 mg (62%) de 2-[3-(*terc*-butildimetilsilaniloxi)-4,4,4-

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trifluoro-1,1-dimetilbutil]piridina como un aceite incoloro.

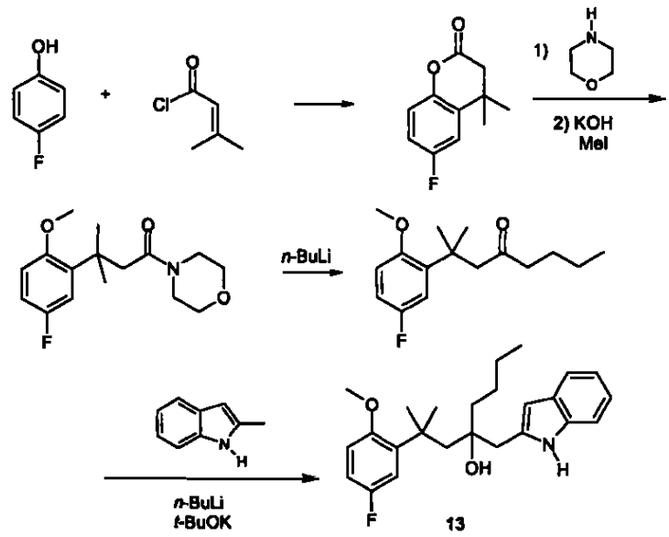
Se agitó a temperatura ambiente durante 2 horas una mezcla de 550 mg (1,58 mmol) de 2-[3-(*terc*-butildimetilsilaniloxi)-4,4,4-trifluoro-1,1-dimetilbutil]piridina en 4,5 ml (4,5 mmol) de fluoruro de tetrabutilamonio (solución 1,0 M en THF). La mezcla se concentró a vacío y el residuo se purificó por cromatografía ultrarrápida proporcionando 367 mg (99%) de 1,1,1-trifluoro-4-metil-4-piridin-2-ilpentan-2-ol como un aceite amarillo claro.

Se diluyó con 2 ml de diclorometano una solución de 516 µl (1,03 mmol, 1,2 eq) de cloruro de oxalilo (solución 2,0 M en diclorometano). A esta solución se añadió una solución de 146 µl (2,06 mmol, 2,4 eq.) de DMSO en 0,2 ml de diclorometano a -60°C y la mezcla se agitó durante 10 minutos a esta temperatura. A continuación se añadió a esta mezcla una solución de 200 mg (0,86 mmol) de 1,1,1-trifluoro-4-metil-4-piridin-2-ilpentan-2-ol en 2 ml de diclorometano a -60°C. La mezcla resultante se agitó a -60°C durante 15 minutos y luego se añadieron 600 µl (4,3 mmol, 5,0 eq.) de trietilamina. Se retiró el baño de enfriamiento y se dejó calentar la mezcla de reacción hasta temperatura ambiente y se inactivó con agua. Se separó la capa orgánica. La capa acuosa se extrajo tres veces con diclorometano. Las capas orgánicas reunidas se secaron sobre sulfato de magnesio, se filtraron y se concentraron a vacío. El residuo se purificó por cromatografía ultrarrápida proporcionando 172 mg (86%) de 1,1,1-trifluoro-4-metil-4-piridin-2-ilpentan-2-ona como un aceite pardo.

Se añadieron gota a gota a -75°C a una solución de 42,4 mg (0,324 mmol, 1,5 eq.) de 2-metilindol en 2 ml de THF, 389 µl (0,972 mmol, 4,5 eq.) de *n*-butil litio (solución 2,5 M en hexanos) y 648 µl (0,648 mmol, 3,0 eq.) de *terc*-butóxido potásico (solución 1,0 M en THF). La mezcla resultante se dejó calentar hasta -20°C durante 30 minutos. La mezcla de reacción se enfrió hasta -75°C y se añadió a esta temperatura una solución de 50 mg (0,216 mmol) de 1,1,1-trifluoro-4-metil-4-piridin-2-ilpentan-2-ona en 1 ml de THF. La mezcla resultante se agitó a esta temperatura durante 30 minutos y luego se inactivó con solución saturada de NH_4Cl. El producto se extrajo en éter y la capa de éter se lavó con agua y salmuera, se secó sobre sulfato de magnesio, se filtró y se concentró a vacío. El residuo se purificó por cromatografía ultrarrápida proporcionando 22 mg (28%) del compuesto del epígrafe como una espuma blanca.

Ejemplo 13: Síntesis de 7-(5-fluoro-2-metoxifenil)-5-(indol-2-ilmetil)-7-metiloctan-5-ol

Se añadió trietilamina (14 ml) gota a gota durante 20 minutos a una solución de 4-fluorofenol (11,2 g) y cloruro de dimetilacriloilo (11,9 g) en éter dietílico (200 ml) enfriado en hielo. Después de otros 30 minutos más la mezcla de reacción se filtró a través de tierra de diatomeas para eliminar el hidrocloruro de trietilamina precipitado. La solución de éter se lavó con agua y salmuera, se secó sobre sulfato sódico y se evaporó proporcionando el éster intermedio bruto (19 g). El éster se disolvió en disulfuro de carbono (50 ml) y se añadió tricloruro de aluminio (19 g) lentamente como un sólido durante 1 hora (reacción exotérmica). La mezcla se dejó agitar a temperatura ambiente a continuación durante toda la noche. El disulfuro de carbono se eliminó en una corriente de nitrógeno. El residuo se inactivó vertiendo sobre hielo y se neutralizó con bicarbonato sódico acuoso. La mezcla se extrajo con éter, y la fase orgánica se secó, se filtró y se evaporó. La cromatografía del residuo sobre una columna de gel de sílice rellena en la parte superior con silicato magnésico activado con FLORISIL® (eluyente: éter-hexanos (95:5) proporcionó la lactona deseada como un aceite que solidificó al triturar con hexanos (rendimiento: 10,5 g).



Se calentaron la lactona y morfolina a 80°C (temperatura del baño) durante 30 minutos. Apareció un producto cristalino. La mezcla se enfrió hasta temperatura ambiente y se trituró con agua. El producto cristalino se recogió por filtración. El producto se suspendió en DMSO (20 ml) y se añadió yoduro de metilo (2 ml). Se añadió una solución de hidróxido potásico (1,2 g) en agua (10 ml) durante 20 minutos (exotermia moderada). Se añadió más yoduro de metilo (0,5 ml) seguido por hidróxido potásico (0,25 g) en agua (5 ml). La mezcla se agitó durante 20 minutos. El producto cristalino se

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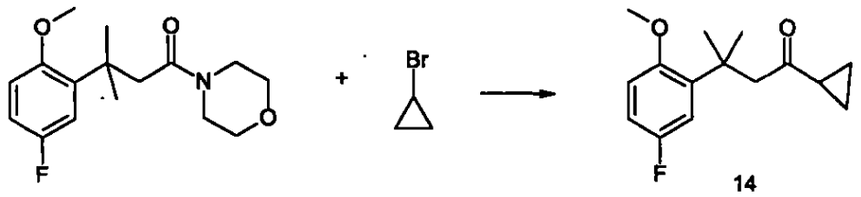
recogió por filtración, se lavó con agua y se secó a vacío a 40°C proporcionando 3-(5-fluoro-2-metoxifenil)-3-metil-1-morfolin-4-ilbutan-1-ona (5,1 g).

Se añadió gota a gota durante 5 minutos *n*-butil litio (2M en pentano, 1 ml) a una solución de la anterior 3-(5-fluoro-2-metoxifenil)-3-metil-1-morfolin-4-ilbutan-1-ona (0,29 g) en THF (2 ml) enfriada hasta -70°C en argon. La mezcla se agitó a -70°C durante 15 minutos y luego se inactivó con EtOH (0,2 ml). Se añadieron agua (1 ml) y EtOAc (2 ml) y la mezcla se calentó hasta temperatura ambiente. La fase orgánica se separó y se lavó con agua, se secó sobre sulfato sódico y se evaporó proporcionando el producto como un aceite (0,26 g).

Se añadió *n*-butil litio (2,5 M en hexano, 1,3 ml) gota a gota a una solución de 2-metilindol (0,13 g) en THF (1 ml) enfriada hasta -70°C en argon. Después de 5 minutos, se añadió *terc*-butóxido potásico (1M en THF, 2 ml) y se retiró el baño de enfriamiento. Después de aproximadamente 5 minutos, apareció un precipitado sólido y la mezcla se volvió a enfriar en un baño de hielo seco/acetona. La cetona anterior (0,24 g) en THF (1 ml) se añadió de una vez y la mezcla se agitó calentando hasta temperatura ambiente durante 1 hora. La reacción se inactivó con EtOH (0,3 ml) y se diluyó con EtOAc. La mezcla se lavó con agua, se secó se filtró y se evaporó. La cromatografía en capa de preparación del residuo (cloruro de metileno como revelador), seguida por una segunda cromatografía en capa de preparación (revelador: EtOAc-hexanos 5:95)) proporcionó el compuesto del epígrafe como un aceite (24 mg).

Los Ejemplos 14-17 ilustran la síntesis de otras cetonas que se pueden usar como intermedios para preparar los compuestos de Fórmula (IB) en procedimientos análogos a los descritos en el Ejemplo 13.

Ejemplo 14: Síntesis de 1-ciclopropil-3-(5-fluoro-2-metoxifenil)-3-metilbutan-1-ona

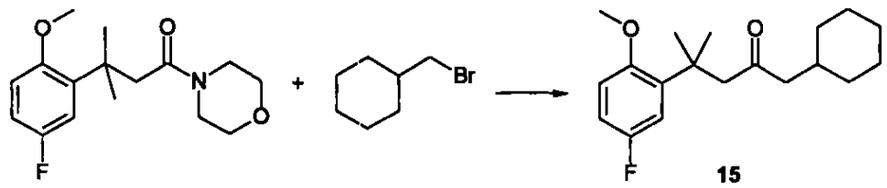


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Se añadió gota a gota durante 5 minutos a una solución de bromuro de ciclopropilo (0,120 g) en THF (0,8 ml) enfriada hasta -70°C, una solución de *terc*-butil litio (1,7 M en pentano, 0,8 ml). La mezcla se agitó a -70°C durante 30 minutos. Se añadió entonces de una vez una solución de 3-(5-fluoro-2-metoxifenil)-3-metil-1-morfolin-4-ilbutan-1-

ona (0,29 g) en THF (1 ml) y la mezcla se agitó durante 30 minutos. La mezcla se inactivó con EtOH (0,3 ml) y se calentó hasta temperatura ambiente. La mezcla se diluyó con EtOAc, se lavó con agua, se secó sobre sulfato sódico, se filtró y se evaporó proporcionando el compuesto del epígrafe como un aceite (0,23 g).

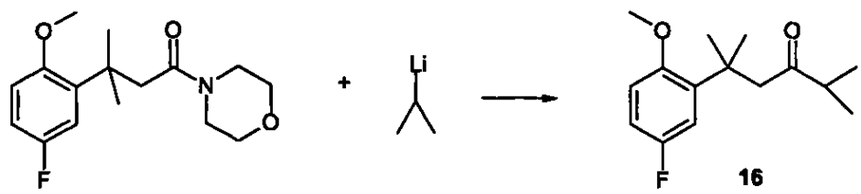
Ejemplo 15: Síntesis de 1-ciclohexil-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ona



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Se añadió gota a gota durante 5 minutos a una solución de bromuro de ciclohexilmetilo (0,26 g) en THF (1 ml) enfriada hasta -70°C en argon, *terc*-butil litio (1,7 M en pentano, 1,8 ml). La mezcla se agitó a -70°C durante 30 minutos. Se añadió de una vez una solución de 3-(5-fluoro-2-metoxifenil)-3-metil-1-morfolin-4-ilbutan-1-ona (0,33 g) en THF (1 ml) y la mezcla se agitó durante 1 hora. La temperatura de reacción se elevó hasta aproximadamente -20°C. La reacción se inactivó con EtOH (0,3 ml) y se calentó hasta temperatura ambiente. La mezcla se diluyó con EtOAc, se lavó con agua, se secó, se filtró y se evaporó. La cromatografía del residuo sobre gel de sílice (eluyente: gradiente de hexanos-cloruro de metileno) proporcionó el compuesto del epígrafe como un aceite (0,2 g).

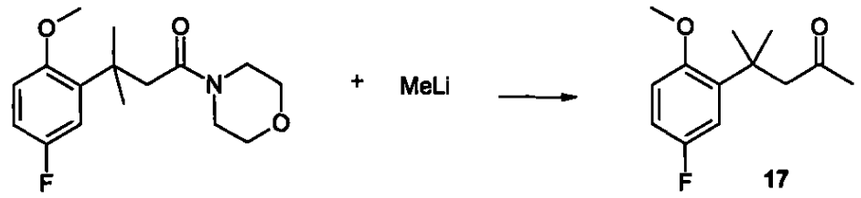
Ejemplo 16: Síntesis de 5-(5-fluoro-2-metoxifenil)-2,5-dimetilhexan-3-ona



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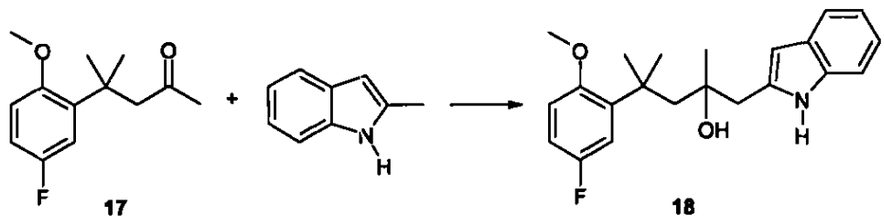
Se añadió isopropil litio (0,7 M en pentano, 3 ml) durante 10 minutos a una solución de 3-(5-fluoro-2-metoxifenil)-3-metil-1-morfolin-4-ilbutan-1-ona (0,45 g) en THF (2 ml) agitada en argon y enfriada en hielo seco/acetona. La mezcla se agitó durante 20 minutos y se inactivó con EtOH (0,3 ml). La mezcla se calentó hasta temperatura ambiente y se añadió 1 ml de agua. La fase orgánica se separó, se lavó, se secó, se filtró y se evaporó. El residuo se fraccionó en una columna corta de gel de sílice (eluyente: hexanos-cloruro de metileno (1:1)) proporcionando el producto como un aceite (0,40 g).

Ejemplo 17: Síntesis de 4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ona



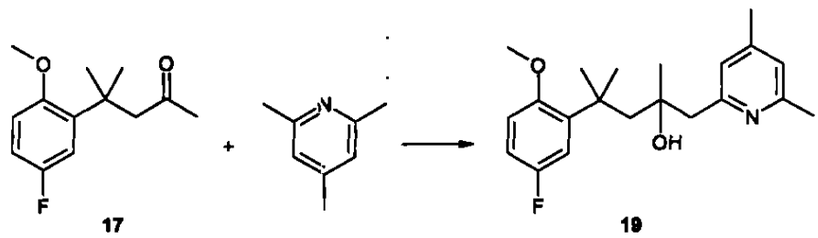
Se añadió metil litio (1,4M en pentano, 2 ml) durante 2 minutos a una solución de 3-(5-fluoro-2-metoxifenil)-3-metil-1-morfolin-4-ilbutan-1-ona (0,59 g) en THF (1 ml) agitada en argon y enfriada en hielo seco/acetona. La mezcla se agitó durante 30 minutos y se inactivó con EtOH (0,3 ml). La mezcla se calentó hasta temperatura ambiente y se añadió 1 ml de agua. La fase orgánica se separó, se lavó, se secó, se filtró y se evaporó. El residuo se fraccionó en una columna corta de gel de sílice (eluyente: hexanos-cloruro de metileno (1:1)), proporcionando el compuesto del epígrafe como un aceite (0,36 g).

Ejemplo 18: Síntesis de 4-(5-fluoro-2-metoxifenil)-2-(indol-2-ilmetil)-4-metilpentan-2-ol



Se añadió *n*-butil litio (2M en pentano, 1,6 ml) a una solución de 2-metilindol (130 mg) en THF (2 ml) agitada en argon y enfriada en hielo seco/acetona. Después de 2 minutos, se añadió *terc*-butóxido potásico (1M en THF, 2 ml) y la mezcla se dejó calentar hasta aproximadamente -20°C. Después de 5 minutos se observó un precipitado y la mezcla se enfrió hasta -70°C. Se añadió de una vez 4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ona (Ejemplo 17) (440 mg) en THF (1,5 ml). Se retiró el baño de enfriamiento y la mezcla se agitó durante 10 minutos y luego se inactivó con EtOH (0,5 ml). La mezcla se diluyó con EtOAc, se lavó con agua, se secó, se filtró y se evaporó. La cromatografía sobre gel de sílice (EtOAc-hexanos (1:9)) proporcionó un producto que solidificó al triturar con hexanos-éter. El sólido se recristalizó en éter-hexanos, se recogió por filtración y se secó a vacío proporcionando 0,11 g del compuesto del epígrafe, p.f. 118°C-120°C.

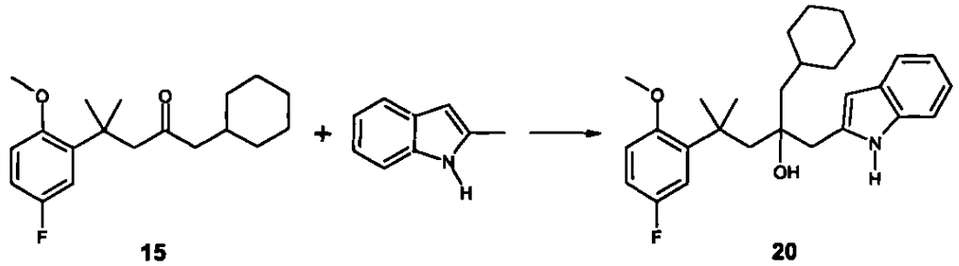
Ejemplo 19: Síntesis de 4-(5-fluoro-2-metoxifenil)-2-(4,6-dimetilpiridin-2-ilmetil)-4-metilpentan-2-ol



17 19

Se añadió gota a gota durante 2 minutos a una solución de 2,4,6-trimetilpiridina (0,14 g) en THF (1 ml) agitada en argon y enfriada hasta -70°C, *terc*-butil litio (1,7M en pentano, 0,75 ml). Después de agitar durante otros 2 minutos más, se añadió de una vez 4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ona (Ejemplo 17) (0,22 g) en THF (0,8 ml). Después de 5 minutos, se inactivó la reacción con EtOH (0,2 ml) y se dejó calentar hasta temperatura ambiente. La mezcla se diluyó con EtOAc, se lavó con agua, se secó, se filtró y se evaporó. La cromatografía del residuo sobre gel de sílice (eluyente: EtOAc-cloruro de metileno (gradiente de 2:98 a 8:92)) proporcionó el producto como un aceite (0,19 g).

Ejemplo 20: Síntesis de 1-ciclohexil-4-(5-fluoro-2-metoxifenil)-2-(indol-2-ilmetil)-4-metilpentan-2-ol

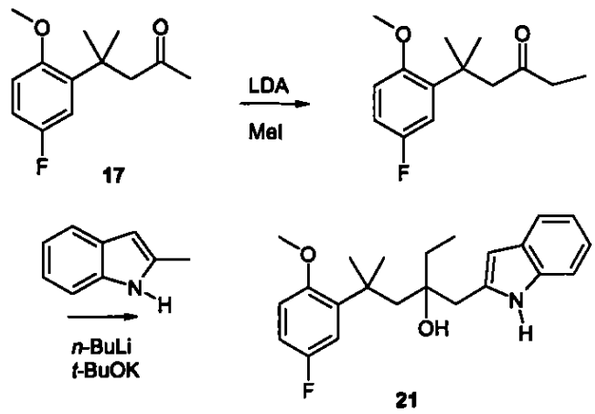


15 20

Se añadió *n*-butil litio (2M en pentano, 0,8 ml) a una solución del 2-metilindol (65 mg) en THF (1 ml) agitado en argon y enfriado en hielo seco/acetona. Después de 2 minutos, se añadió *terc*-butóxido potásico (1M en THF, 1 ml) y la mezcla se dejó calentar hasta aproximadamente -20°C. Después de 5 minutos, se observó un precipitado y la mezcla se enfrió hasta -70°C. Se añadió gota a gota 1-ciclohexil-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ona (Ejemplo 15) (100 mg) en THF (1 ml) y la mezcla se agitó durante 20 minutos a -70°C. La reacción se inactivó con EtOH (0,5 ml). La mezcla se diluyó con EtOAc, se lavó con agua, se secó, se filtró y se evaporó. La cromatografía sobre gel de sílice (cloruro de metileno-hexanos (1:2)) proporcionó el compuesto del epígrafe como un aceite (0,095 g).

Ejemplo 21: Síntesis de 5-(5-fluoro-2-metoxifenil)-3-(indol-2-ilmetil)-5-metilhexan-

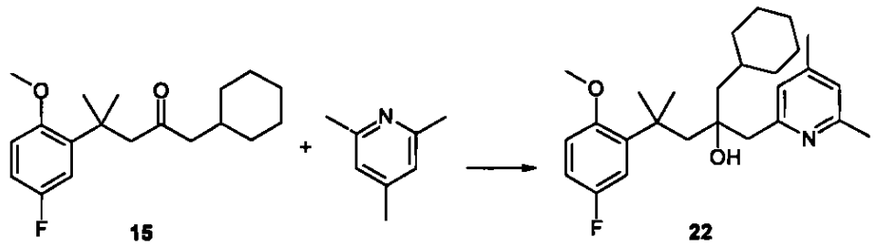
3-ol



Se añadió gota a gota una solución de 4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ona (0,44 g) en THF (1 ml) a una solución de diisopropilamida de litio (2 M en THF-hexanos-etilbenceno, 1,0 ml) en 1 ml de THF en argon enfriada hasta -70°C. La mezcla se agitó durante 30 minutos y luego se añadió gota a gota una solución de yoduro de metilo (0,28 g) en THF (0,5 ml) y la mezcla se agitó alcanzando la temperatura ambiente durante toda la noche. La mezcla se diluyó en hexanos, se lavó con agua, se secó, se filtró y se evaporó. La cromatografía del residuo sobre gel de sílice (hexanos-cloruro de metileno 1:4-1:1)) proporcionó la hexan-3-ona deseada como un aceite (0,20 g).

Se añadió *n*-butil litio (2M en pentano, 0,8 ml) a una solución de 2-metilindol (64 mg) en THF (1 ml) agitada en argon enfriada sobre hielo seco/acetona. Después de 2 minutos, se añadió *terc*-butóxido potásico (1M en THF, 1 ml) y la mezcla se dejó calentar hasta aproximadamente -20°C. Después de aproximadamente 5 minutos, se observó un precipitado y la mezcla se enfrió hasta -70°C. La hexan-3-ona (100 mg) en THF (1 ml) se añadió gota a gota y se agitó la mezcla durante 20 minutos a -70°C. La reacción se inactivó con EtOH (0,5 ml). La mezcla se diluyó con EtOAc, se lavó con agua, se secó, se filtró y se evaporó. La cromatografía sobre gel de sílice (cloruro de metileno-hexanos (1:2)) proporcionó el compuesto del epígrafe como un aceite (0,062 g).

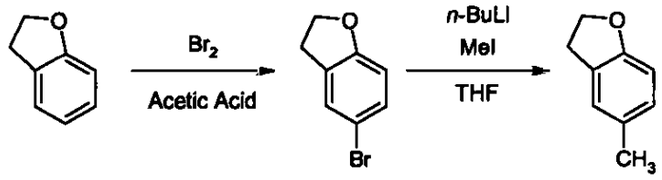
Ejemplo 22: Síntesis de 1-ciclohexil-2-(4,6-dimetilpiridin-2-ilmetil)-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol



Se añadió gota a gota durante 3 minutos *terc*-butil litio (1,7 M en pentano, 0,55 ml) a una solución de colidina (0,113 g) en THF (1 ml) enfriada hasta -70°C. La mezcla se agitó durante 5 minutos y luego se añadió gota a gota 1-ciclohexil-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ona (Ejemplo 15) (0,095 g) en THF (0,5 ml). Después de 10 minutos a -70°C, la reacción se inactivó mediante adición de EtOH (0,2 ml) y se calentó hasta temperatura ambiente. La mezcla se diluyó con EtOAc, se lavó con agua, se secó sobre sulfato sódico, se filtró y se evaporó. El residuo se fraccionó por cromatografía en capa de preparación (revelador: cloruro de metileno-EtOAc (99:1)) seguida por cromatografía en capa de preparación (revelador: hexanos-cloruro de metileno-EtOH (1:1:0,01)) proporcionando el compuesto del epígrafe como un aceite (73 mg).

Los Ejemplos 23 y 24 ilustran la síntesis de dihidrobenzofuranos sustituidos. Estos se pueden convertir en intermedios de trifluorometilcetona por el procedimiento descrito en el Ejemplo 1 para 4-fluoroanisol.

Ejemplo 23: Síntesis de 5-metil-2,3-dihidrobenzofurano



23

Se añadieron gota a gota durante un período de 10 minutos 4 ml (78 mmol) de bromo en 6 ml de ácido acético a una solución enfriada (10°C) de 10 g (83 mmol) de 2,3-dihidrobenzofurano en 50 ml de ácido acético. Después de 1 hora, la mezcla se basificó mediante el vertido cuidadoso de la mezcla de reacción en solución de bicarbonato sódico acuosa saturada/sólida y agitando durante toda la noche. La mezcla se extrajo entonces con tres porciones de 100 ml de EtOAc. Las capas orgánicas reunidas se lavaron con dos porciones de 50 ml de bicarbonato sódico acuoso saturado, tres porciones de 50 ml de salmuera, se secaron sobre sulfato de magnesio, se filtraron y se

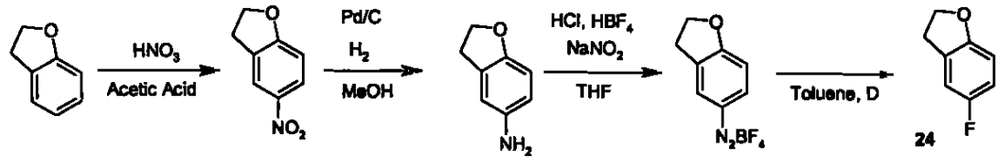
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concentraron proporcionando un aceite amarillo. El aceite se diluyó con hexanos y se hizo pasar a través de un lecho de gel de sílice en un embudo de 600 ml eluyendo con hexanos, proporcionando un sólido blanco que se diluyó con hexanos fríos (hielo seco-acetona) y se recogió por filtración proporcionando 4,7 g (28%) de 5-bromo-2,3-dihidrobenzofurano como un sólido blanco, p.f. 45°C-48°C. El filtrado se concentró proporcionando 5,1 g de 5-bromo-2,3-dihidrobenzofurano que tenía una pureza del 70%.

Se añadieron 13,4 ml (26,8 mmol) de una solución 2,0 M de *n*-butil litio en pentano a una solución fría (-78°C) de 5,2 g (26,12 mmol) de 5-bromo-2,3-dihidrobenzofurano en THF anhidro. Después de 10 minutos, se añadieron gota a gota 4 ml (64,25 mmol) de yodometano. Después de la adición, se retiró el baño de enfriamiento y se agitó la mezcla a temperatura ambiente. Después de 2 horas, la mezcla se diluyó con 40 ml de cloruro de amonio acuoso saturado y se extrajo con tres porciones de 30 ml de EtOAc. Las capas orgánicas reunidas se lavaron con tres porciones de 30 ml de salmuera, se secaron sobre sulfato de magnesio, se filtraron y se concentraron proporcionando 3,7 g de un aceite amarillo. El aceite se destiló a vacío (Kugelrohr) a 70°C-80°C proporcionando 1,6 g (45%) del compuesto del epígrafe que se usó sin purificación adicional.

La siguiente cetona se preparó usando el procedimiento descrito en el Ejemplo 1: 1,1,1-Trifluoro-4-metil-4-(5-metil-2,3-dihidrobenzofuran-7-il)pentan-2-ona.

Ejemplo 24: Síntesis de 5-Fluoro-2,3-dihidrobenzofuran



24

Se añadió una cuarta parte de 4,5 ml (0,227 mol) de ácido nítrico acuoso al 70% gota a gota a una solución de 25,5 g (0,212 mol) de 2,3-dihidrobenzofurano en 175 ml de ácido acético. La reacción se controló por TLC (EtOAc-hexanos, 15:85). La mezcla se calentó hasta 70°C, momento en el que comenzó la reacción. Se añadió entonces el resto del ácido nítrico mientras se mantenía la reacción a 70°C. Después de 30 minutos, se enfrió la reacción y se vertió en 1,5 l de agua helada. Se recogió el sólido negro por filtración lavando con agua. El sólido se repartió entre 500 ml de bicarbonato sódico acuoso saturado y 150 ml de EtOAc. Se separó la capa acuosa y se extrajo con tres porciones de 150 ml de EtOAc. Las capas orgánicas reunidas se lavaron con tres

porciones de 100 ml de bicarbonato sódico acuoso saturado, 100 ml de cloruro amónico acuoso saturado, 100 ml de salmuera, se secaron sobre sulfato de magnesio, se filtraron y se concentraron proporcionando un aceite/sólido rojo. La mezcla se disolvió en diclorometano y se hizo pasar a través de un lecho de gel de sílice, eluyendo con diclorometano y se concentró. La mezcla roja resultante se trituró con éter-hexanos (1:1) y se filtró proporcionando 10,5 g (29%) de 5-nitro-2,3-dihidrobenzofurano como un sólido color castaño.

Se añadieron 350 mg de paladio al 10% sobre carbón a una suspensión de 10,3 g (62,37 mmol) de 5-nitro-2,3-dihidrobenzofurano en 50 ml de MeOH y 10 ml de diclorometano y la mezcla se colocó en gas hidrógeno a 370 kPa. La absorción de gas fue evidente durante los primeros treinta minutos. Después de 18 horas, se filtró la mezcla a través de tierra de diatomeas y se concentró proporcionando 8,2 g de 2,3-dihidrobenzofuran-5-ilamina como un sólido gris que se usó sin purificación adicional.

Se añadieron 6 ml de HCl acuoso concentrado en varias porciones a una solución de 8,2 g (60,66 mmol) de 2,3-dihidrobenzofuran-5-ilamina en 250 ml de THF. Se añadieron al precipitado blanco resultante 11 ml de ácido tetrafluorobórico gota a gota. La mezcla se enfrió entonces (-15°C) y se añadieron gota a gota 4,7 g (68,12 mmol) de nitrito sódico en 20 ml de agua. La suspensión viró a gris intenso, se hizo homogénea y luego se formó un precipitado. La mezcla se agitó durante 30 minutos a -15°C y luego se recogió el sólido por filtración lavando con agua fría, etanol frío y éter frío. El sólido se secó haciendo vacío a través de la torta del filtro proporcionando 9,7 g (68%) de sal tetrafluoroborato de 5-diazonio-2,3-dihidrobenzofurano, que se usó sin purificación adicional.

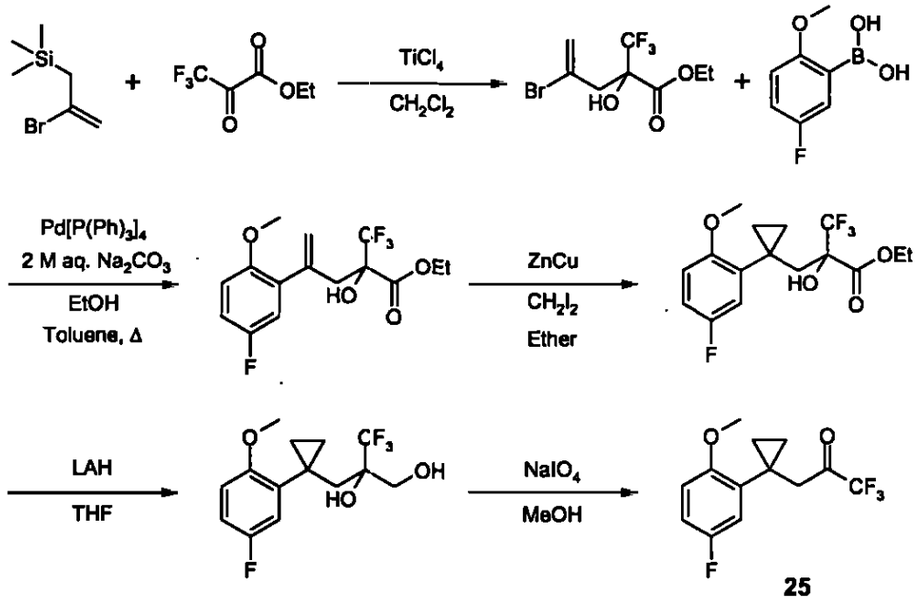
Se calentó a reflujo durante 1 hora una suspensión de 9,7 g (41,46 mmol) del la sal de diazonio tetrafluoroborato anterior en xilenos. La mezcla se enfrió entonces y se diluyó con 200 ml de bicarbonato sódico acuoso saturado. Se separó la capa acuosa y se extrajo con tres porciones de 50 ml de bicarbonato sódico acuoso, 50 ml de salmuera, se secó sobre sulfato de magnesio, se filtró y se concentró proporcionando un aceite. El aceite bruto se sometió a cromatografía sobre gel de sílice usando EtOAc-hexanos (0:100, luego 0,5:99,5) proporcionando 2,6 g (45%) del compuesto del epígrafe.

Usando el procedimiento descrito en el Ejemplo 1, se preparó la siguiente cetona: 1,1,1-Trifluoro-4-(5-fluoro-2,3-dihidrobenzofuran-7-il)-4-metilpentan-2-ona.

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Ejemplo 25: Síntesis de 1,1,1-trifluoro-3-[1-(5-fluoro-2-metoxifenil)ciclopropil]propan-2-ona

Se añadieron 30 ml (30 mmol) de una solución 1M de tetracloruro de titanio en diclorometano durante un período de 10 minutos a una solución fría (-78°C) de 5,2 ml (30,18 mmol) de 2-bromoaliltrimetilsilano y 5,3 g (31,16 mmol) de trifluoropiruvato de etilo en 75 ml de diclorometano. Se retiró a continuación el baño de enfriamiento y la mezcla se calentó hasta temperatura ambiente. Después de 3 horas, la mezcla se añadió cuidadosamente a 100 ml de cloruro amónico acuoso saturado y se filtró a través de tierra de diatomeas, lavando con diclorometano. El diclorometano se separó y la capa acuosa se extrajo con tres porciones de 50 ml de diclorometano. Las capas orgánicas reunidas se lavaron con dos porciones de 50 ml de bicarbonato sódico acuoso saturado, 50 ml de salmuera, se secaron sobre sulfato de magnesio, se filtraron y se concentraron proporcionando 6,7 g (76%) de éster etílico del ácido 4-bromo-2-hidroxi-2-trifluorometilpent-4-enoico como un aceite amarillo que se usó sin purificación adicional.



25

Se calentó a reflujo una mezcla de 500 mg (1,71 mmol) de éster etílico del ácido 4-bromo-2-hidroxi-2-trifluorometilpent-4-enoico, 509 mg (3 mmol) de ácido 3-fluoro-5-metoxifenilborónico y 25 mg (0,022 mmol) de tetrakis(trifenilfosfina)paladio(0) en 4 ml de tolueno, 2 ml de etanol y 1 ml de carbonato sódico acuoso 2 M. Después de 24 horas, la mezcla se enfrió y se diluyó con cloruro amónico acuoso saturado y se extrajo con

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tres porciones de 10 ml de EtOAc. Las capas orgánicas reunidas se lavaron con tres porciones de 5 ml de salmuera, se secaron sobre sulfato magnésico, se filtraron y se concentraron. El producto bruto solidificó en reposo y se adsorbió sobre gel de sílice y se sometió a cromatografía sobre gel de sílice usando EtOAc-hexanos (0:100, luego 0,5:99,5, luego 1:99, luego 2:98) proporcionando el producto parcialmente purificado. La trituración con éter-hexanos separó un subproducto insoluble. El filtrado se sometió a cromatografía sobre gel de sílice usando diclorometano-hexanos (5:95, luego 1:9, luego 15:85, luego 2:8, luego 3:7, luego 4:6) proporcionando 280 mg (48%) de éster etílico del ácido 4-(5-fluoro-2-metoxifenil)-2-hidroxi-2-trifluorometilpent-4-enoico como un aceite que solidificó en reposo.

Se añadieron, gota a gota, 500 µl (6,20 mmol) de diyodometano a una solución de 620 mg (1,84 mmol) de éster etílico del ácido 4-(5-fluoro-2-metoxifenil)-2-hidroxi-2-trifluorometilpent-4-enoico, 475 mg de par de cinc cobre y un cristal de yodo en éter anhidro en un tubo herméticamente cerrado calentado hasta 55°C. La reacción se controló por TLC en diclorometano-hexanos (1:1) o éter-hexanos (2:8). Después de 18 horas, la mezcla se enfrió, se diluyó con EtOAc y se filtró a través de tierra de diatomeas. El filtrado se lavó con tres porciones de 10 ml de bicarbonato sódico acuoso saturado, se secó sobre sulfato de magnesio, se filtró y se concentró. El material bruto se adsorbió sobre gel de sílice y se sometió a cromatografía sobre gel de sílice usando éter-hexanos (0:100, luego 1:99, luego 2:98) proporcionando 494 mg (76%) de éster etílico del ácido 3,3,3-trifluoro-2-[1-(5-fluoro-2-metoxifenil)ciclopropilmetil]-2-hidroxipropionico.

Se añadieron 98 mg (2,58 mmol) de hidruro de litio y aluminio en varias porciones a una solución enfriada (0°C) de 400 mg (1,14 mmol) de éster etílico del ácido 3,3,3-trifluoro-2-[1-(5-fluoro-2-metoxifenil)ciclopropilmetil]-2-hidroxipropionico en 5 ml de THF anhidro. Se retiró a continuación el baño de enfriamiento y la mezcla se agitó a temperatura ambiente. Después de 4,5 horas, la mezcla se enfrió en un baño de agua helada y se inactivó cuidadosamente con agua, se secó sobre sulfato de magnesio y se filtró a través de tierra de diatomeas, lavando con EtOAc proporcionando 278 mg (78%) del compuesto del epígrafe que se usó sin purificación adicional. La torta del filtro se repartió entre 15 ml de ácido clorhídrico acuoso 1N y se extrajo con tres porciones de 10 ml de EtOAc. Las capas orgánicas reunidas se lavaron con dos porciones de 10 ml de ácido clorhídrico acuoso 1N, 10 ml de salmuera y dos porciones de 10 ml de bicarbonato sódico acuoso saturado, se secaron sobre sulfato de magnesio, se filtraron y se concentraron proporcionando además 32 mg (8,9%) de 3,3,3-trifluoro-2-[1-(5-fluoro-

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2-metoxifenil)ciclopropilmetil]propano-1,2-diol.

Se añadieron 1,5 g (7,01 mmol) de peryodato sódico a una solución de 310 mg (1,01 mmol) de 3,3,3-trifluoro-2-[1-(5-fluoro-2-metoxifenil)ciclopropilmetil]propano-1,2-diol en 15 ml de MeOH. Después de 7 horas, se concentró la mezcla y el residuo se diluyó con hexanos y se filtró a través de tierra de diatomeas. El residuo bruto se sometió a cromatografía sobre gel de sílice usando hexanos para cargar la muestra y luego eluyendo con EtOAc-hexanos (0:100, luego 0,25:99,75, luego 0,5:99,5, luego 1:99) proporcionando 200 mg del compuesto del epígrafe como un aceite transparente.

Las siguientes trifluorometil cetonas también se prepararon por el procedimiento del Ejemplo 25:

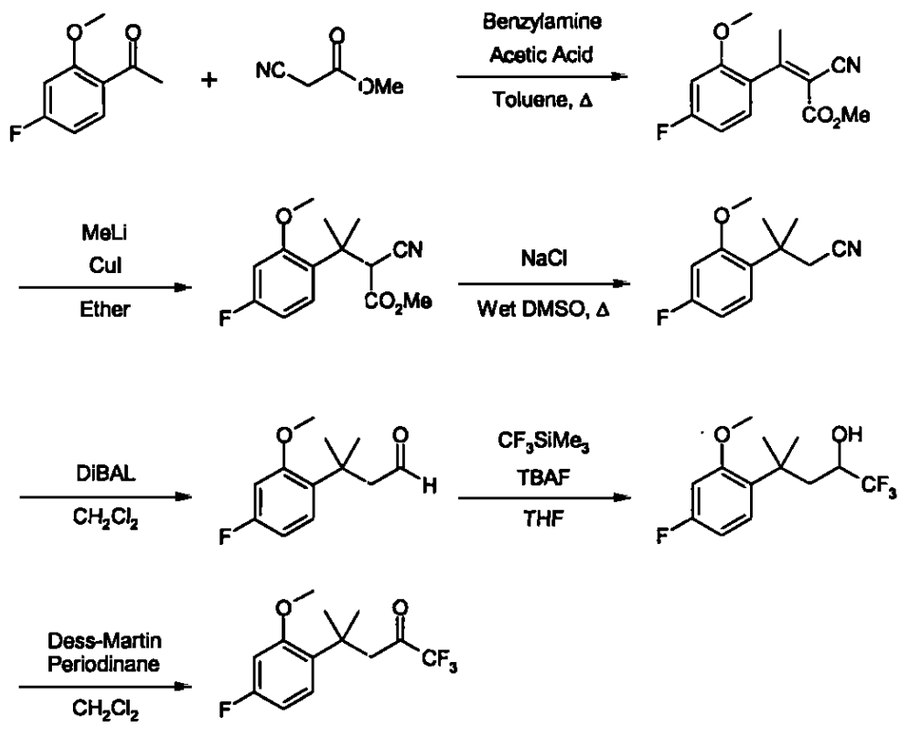
1,1,1-Trifluoro-3-[1-(2-trifluorometoxifenil)ciclopropil]propan-2-ona;

3-[1-(2,5-Difluorofenil)ciclopropil]-1,1,1-trifluoropropan-2-ona; y

1,1,1-Trifluoro-3-[1-(4-fluorofenil)ciclopropil]propan-2-ona.

Ejemplo 26: Síntesis de 1,1,1-trifluoro-4-(4-fluoro-2-metoxifenil)-4-metilpentan-2-ona

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26

Se añadió una mezcla de 19,54 g (116 mmol) de 4-fluoro-2-metoxiacetofenona, 15,29 ml (174 mmol) de cianoacetato de metilo, 1,42 ml (13 mmol) de bencilamina y 6,6 ml de ácido acético en 170 ml de tolueno a un matraz de fondo de redondo dotado de una trampa de Dean-Stark y la mezcla se calentó hasta reflujo. La reacción se controló por TLC (EtOAc-hexanos, 2:8). Después de 18 horas, la reacción se enfrió y se concentró a vacío proporcionando un aceite naranja oscuro. El aceite bruto se destiló a 130°C a vacío (Kugelrohr) para eliminar la 4-fluoro-2-metoxiacetofenona sin reaccionar. El producto bruto se hizo pasar entonces a través de un lecho de gel de sílice usando EtOAc al 10% en una mezcla 1:1 de diclorometano en hexanos, proporcionando 27,64 g (95%) de éster metílico del ácido 2-ciano-3-(4-fluoro-2-metoxifenil)but-2-enoico como un aceite naranja claro que era una mezcla de isómeros geométricos.

Se añadieron 26 ml (41,60 mmol) de una solución 1,6 M de metil litio en éter durante un período de 15 minutos a una suspensión enfriada (0°C) de 4,3 g (22,58 mmol) de yoduro de cobre (I) (purificado por extracción de Soxhlet con THF) en 100 ml de éter dietílico. Después de la adición, la mezcla se agitó durante 10 minutos y luego se enfrió hasta -25°C y se añadió durante un período de 20 minutos una solución de 4,0 g (15,19 mmol) de éster metílico del ácido 2-ciano-3-(4-fluoro-2-metoxifenil)but-2-enoico en 50

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ml de éter dietílico. La mezcla se agitó a -25°C durante 30 minutos y luego se dejó calentar hasta temperatura ambiente. La reacción se controló por RMN de protón. Después de 1,5 horas, se repartió una parte alícuota entre EtOAc y HCl acuoso 1N indicando que el material de partida había desaparecido y estaba presente el producto deseado. La reacción se vertió cuidadosamente en salmuera y luego se añadió cloruro amónico acuoso saturado, seguido por HCl acuoso 1N y EtOAc. La mezcla se filtró a través de tierra de diatomeas y se separó la capa acuosa y se extrajo con tres porciones de 50 ml de EtOAc. Las capas orgánicas reunidas se lavaron con 30 ml de HCl acuoso 1N, 30 ml de salmuera y tres porciones de 25 ml de bicarbonato sódico acuoso saturado, se secaron sobre sulfato de magnesio, se filtraron y se concentraron proporcionando 4,2 g (99%) de éster metílico del ácido 2-ciano-3-(4-fluoro-2-metoxifenil)-3-metilbutírico.

Se calentó hasta reflujo una mezcla de 4,2 g (15,03 mmol) de éster metílico del ácido 2-ciano-3-(4-fluoro-2-metoxifenil)-3-metilbutírico y 2,5 g (42,77 mmol) de cloruro sódico en 40 ml de DMSO con 2 ml de agua. La formación de gas fue claramente evidente al comienzo de la reacción. Después de 4 horas, la reacción se enfrió y se diluyó con 100 ml de salmuera y se extrajo con cuatro porciones de 75 ml de EtOAc. Las capas orgánicas reunidas se lavaron con seis porciones de 50 ml de salmuera, se secaron sobre sulfato de magnesio, se filtraron y se concentraron proporcionando un aceite que solidificó a vacío. El sólido color castaño se trituró con hexanos y se recogió por filtración proporcionando 2,52 g (81%) de 3-(4-fluoro-2-metoxifenil)-3-metilbutironitrilo, p.f. 80°C-83°C.

Se añadieron 20 ml (20 mmol) de una solución 1M de hidruro de diisobutilaluminio en diclorometano durante un período de 10 minutos a una solución enfriada (-40°C) de 2 g (9,65 mmol) de 3-(4-fluoro-2-metoxifenil)-3-metilbutironitrilo en 20 ml de diclorometano. La mezcla se dejó enfriar hasta temperatura ambiente a continuación. Después de 4 horas, la mezcla se añadió cuidadosamente a HCl acuoso 1N y se concentró a vacío para eliminar el diclorometano. El residuo se extrajo con tres porciones de 40 ml de EtOAc. Las capas orgánicas reunidas se lavaron con 30 ml de HCl acuoso 1N, dos porciones de 30 ml de salmuera, 30 ml de bicarbonato sódico acuoso saturado, se secaron sobre sulfato de magnesio, se filtraron y se concentraron proporcionando 1,89 g (93%) de 3-(4-fluoro-2-metoxifenil)-3-metilbutiraldehído como un aceite que se usó sin purificación adicional.

Se añadieron 25 ml (12,5 mmol) de una solución 0,5 M de trimetil(trifluorometil)silano en tetrahidrofurano y 2 ml de una solución 1M de fluoruro de tetrabutilamonio en

tetrahidrofurano durante un período de 2 minutos a 1,89 g (8,99 mmol) de 3-(4-fluoro-2-metoxifenil)-3-metilbutiraldehído. La mezcla se agitó durante 30 minutos y luego se añadieron 8 ml más (8 mmol) de una solución 1M de fluoruro de tetrabutilamonio. La mezcla se diluyó a continuación con agua y se extrajo con tres porciones de 25 ml de HCl acuoso 1N, tres porciones de 20 ml de salmuera y tres porciones de 20 ml de bicarbonato sódico acuoso saturado, se secaron sobre sulfato de magnesio, se filtraron y se concentraron proporcionando 2,78 g de 1,1,1-trifluoro-4-(4-fluoro-2-metoxifenil)-4-metilpentan-2-ol como un aceite. El aceite se secó a alto vacío hasta peso constante 2,36 g (93%) y se usó sin purificación adicional.

Se añadieron 4,96 (11,70 mmol) de peryodinano de Dess-Martin a una solución de 2,3 g (8,42 mmol) de 1,1,1-trifluoro-4-(4-fluoro-2-metoxifenil)-4-metilpentan-2-ol en 40 ml de diclorometano. Después de 1 hora, la mezcla se concentró y se diluyó con éter-hexanos (1:9) y se filtró a través de un lecho de gel de sílice, lavando con éter-hexanos (1:1). El uso de un segundo lecho de gel de sílice lavando con EtOAc-hexanos (1:9) proporcionó el compuesto del epígrafe como un aceite. El producto se secó a vacío hasta peso constante de 2 g (85%).

Las siguientes trifluorometil cetonas también se prepararon por el procedimiento del Ejemplo 26:

4-(3,5-Dimetoxifenil)-1,1,1-trifluoro-4-metilpentan-2-ona;

1,1,1-Trifluoro-4-(1-metoxinaftalen-2-il)-4-metilpentan-2-ona;

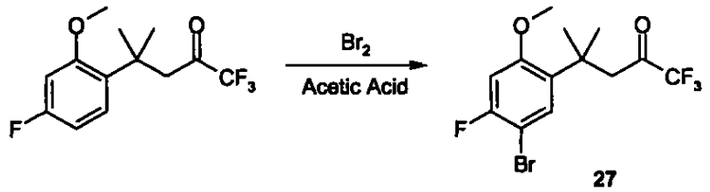
1,1,1-Trifluoro-4-metil-4-naftalen-2-ilpentan-2-ona;

1,1,1-Trifluoro-4-(3-metoxifenil)-4-metilpentan-2-ona; y

1,1,1-Trifluoro-4-metil-4-(3-trifluorometilfenil)pentan-2-ona.

Ejemplo 27: Síntesis de 4-(5-bromo-4-fluoro-2-metoxifenil)-1,1,1-trifluoro-4-metilpentan-2-ona

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Se añadieron 70 µl (1,35 mmol) de bromo a una solución de 300 mg (1,078 mmol) de 1,1,1-trifluoro-4-(4-fluoro-2-metoxifenil)-4-metilpentan-2-ona (Ejemplo 26) en 0,5 ml de ácido acético. La reacción se controló por TLC (EtOAc-hexanos (1:9)) repartiendo una alícuota entre bicarbonato sódico acuoso saturado y EtOAc. Se observó un producto nuevo ligeramente más polar. La reacción se basificó con bicarbonato sódico acuoso saturado y se extrajo con tres porciones de 15 ml de EtOAc. Las capas orgánicas reunidas se lavaron con dos porciones de 10 ml de bicarbonato sódico acuoso saturado y 10 ml de salmuera, se secaron sobre sulfato de magnesio, se filtraron y se concentraron. El residuo se disolvió en hexanos y se hizo pasar a través de un lecho de gel de sílice, eluyendo con EtOAc-hexanos (0,5:99,5) proporcionando 375 mg (97%) del compuesto del epígrafe.

Los siguientes compuestos se prepararon por el procedimiento del Ejemplo 27.

4-(5-Bromo-2,3-dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metilpentan-2-ona; y

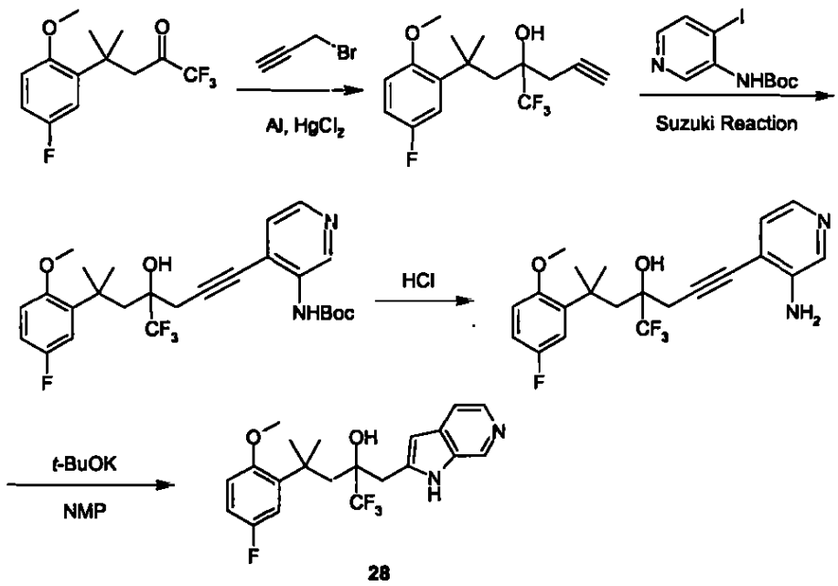
4-(7-Bromo-2,3-dihidrobenzofuran-5-il)-1,1,1-trifluoro-4-metilpentan-2-ona.

Ejemplo 28: Síntesis de 1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol

Se preparó amalgama de aluminio a partir de una hoja de aluminio (1,16 g, 14,4 mmol) y cloruro mercúrico (12 mg, cantidad catalítica) en THF seco (20 ml) agitando intensamente la mezcla a temperatura ambiente durante una hora en atmósfera de argon. Se añadió lentamente una solución de bromuro de propargilo (4,80 ml, 80 % en peso en tolueno, 43,1 mmol) en THF seco (25 ml) a una suspensión agitada mantenida a una temperatura de 30°C-40°C y, después de la adición, se continuó agitando a 40°C hasta que se obtuvo una solución color gris oscuro (aproximadamente 1 hora). La solución de sesquibromuro de propargil aluminio se añadió a una solución de trifluorometilcetona (4,0 g, 14,4 mmol) en éter seco (150 ml) a -78°C. La mezcla de reacción se agitó a esta temperatura durante 3 horas y luego se dejó calentar hasta temperatura ambiente, momento en el que se agitó durante 12 horas. La mezcla de reacción se vertió a

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continuación en 20 ml de agua helada y se extrajo con cuatro porciones de 30 ml de éter. Los extractos reunidos se lavaron con 20 ml de salmuera, se secaron sobre sulfato de magnesio y se concentraron. El aceite residual se sometió a cromatografía en columna sobre gel de sílice proporcionando el compuesto propargilado puro como un aceite.



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Se agitó a temperatura ambiente durante 20 horas una mezcla del intermedio de acetileno anterior (656 mg, 2,06 mmol), éster *terc*-butílico del ácido (4-yodopiridin-3-il)-carbámico (600 mg, 1,87 mmol) (véase T.A. Kelly *et al.*, J. Org. Chem., 1995, 60, 1877), catalizador de cloruro de bis(trifenilfosfina)paladio(II) (72 mg, 0,1 mmol) y yoduro de cobre (I) (39 mg, 0,2 mmol) en trietilamina anhidra (6 ml) y DMF seco (1 ml). La mezcla de reacción se diluyó a continuación con 50 ml de éter y se lavó con 20 ml de solución de cloruro amónico acuoso saturado y 20 ml de salmuera. La capa orgánica se secó sobre sulfato de magnesio y se concentró a vacío. La cromatografía en columna sobre gel de sílice con hexanos-EtOAc (5:1 a 1:1) proporcionó el éster *terc*-butílico del ácido {4-[6-(5-fluoro-2-metoxifenil)-4-hidroxi-6-metil-4-trifluorometilhept-1-inil]piridin-3-il}carbámico como una espuma.

Se trató el éster *terc*-butílico anterior (480 mg, 0,94 mmol) con una solución de cloruro de hidrógeno (2M en éter, 15 ml) y se agitó a temperatura ambiente durante 6 horas. A continuación, se concentró la solución a vacío proporcionando la amina bruta como un

aceite, que se trituró con hexanos proporcionando la amina como un sólido amarillo.

Se añadió *t*-BuOK (449 mg, 112 mmol) a la amina bruta producto anterior (742 mg, 1,81 mmol) en 1-metil-2-pirrolidinona anhidra (NMP) (7 ml) y la mezcla se agitó en atmósfera de argon a temperatura ambiente durante 24 horas. La mezcla se diluyó con 30 ml de éter y se lavó con cuatro porciones de 10 ml de agua y las capas acuosas reunidas se volvieron a extraer con 20 ml de éter, mientras que las capas orgánicas reunidas se lavaron con 10 ml de salmuera, se secaron sobre sulfato de magnesio y se concentraron a vacío. El aceite residual se sometió a cromatografía en columna sobre gel de sílice (cloruro de metileno-MeOH del 1% al 10%), proporcionando 1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol en forma de cristales amarillentos.

Se llevó a cabo la resolución a los enantiómeros (+) y (-) por HPLC quiral en una columna CHIRALCEL™ OD eluyendo con isopropanol del 15% al 25% -hexanos.

Determinación de las propiedades biológicas

Se evaluaron los compuestos de la invención para determinar la unión al receptor de esteroides por un ensayo de unión competitiva con polarización de fluorescencia. Las descripciones detalladas para la preparación del complejo receptor de glucocorticoides recombinante (GR) usado en el ensayo se describen en la solicitud provisional de Estados Unidos nº 60/291,877, presentada el 18 de mayo de 2001 e incorporada en la presente memoria como referencia en su totalidad. La preparación de la sonda de dexametasona marcada con tetrametil rodamina (TAMRA) se llevó a cabo usando un procedimiento convencional de la bibliografía (M. Pons *et al.*, J. Steroid Biochem., 1985, 22, págs. 267-273).

A. Ensayo de unión competitiva al receptor de glucocorticoides

Etapa 1. Caracterización de la sonda fluorescente

Se miden en primer lugar las longitudes de onda para la máxima excitación y emisión de la sonda fluorescente. Un ejemplo de dicha sonda es dexametasona marcada con rodamina (TAMRA).

Se determinó a continuación la afinidad de la sonda por el receptor de esteroides en un experimento de valoración. Se midió el valor de polarización de fluorescencia de la sonda en un tampón de ensayo en un fluorómetro SLM-8100 usando valores máximos de excitación y emisión descritos antes. Se añadieron alícuotas del lisado del vector de

expresión y se midió la fluorescencia después de cada adición hasta que no se observó cambio en el valor de la polarización. Se usó análisis de regresión por mínimos cuadrados no lineal para calcular la constante de disociación de la sonda a partir de los valores de polarización obtenidos para la unión del lisado a la sonda.

Etapa 2. Rastreo de inhibidores de unión a la sonda

Este ensayo usa polarización por fluorescencia (FP) para cuantificar la capacidad de los compuestos de ensayo para competir con dexametasona marcada con tetrametil rodamina (TAMRA) para la unión al complejo receptor de glucocorticoides humano (GR) preparado a partir del sistema de expresión de un insecto. El tampón de ensayo comprendía: TES 10 mM, KCl 50 mM, $Na_2MoO_4 \cdot 2H_2O$ 20 mM, EDTA 1,5 mM, CHAPS al 0,04% p/v, glicerol al 10% v/v, ditiotreitol 1 mM, pH 7,4. Los compuestos de ensayo se disolvieron hasta 1 mM en DMSO puro y luego se diluyeron adicionalmente hasta 10x la concentración de ensayo en tampón de ensayo suplementado con DMSO al 10% v/v. Los compuestos de ensayo se diluyeron en serie a concentraciones de ensayo 10x en tampón que contenía DMSO al 10% en placas de polipropileno de 96 pocillos. Las mezclas para la reacción de unión se prepararon en placas de microvaloración de 96 pocillos negras Dynex mediante adición secuencial de los siguientes componentes de ensayo a cada pocillo: 15 µl de solución de compuesto de ensayo 10x, 85 µl de lisado de baculovirus que contenía GR diluido 1:170 en tampón de ensayo y 50 µl de dexametasona marcada con TAMRA 15 nM. Los controles positivos eran mezclas de reacción que no contenían compuesto de ensayo; los controles negativos (blancos) eran mezclas de reacción que contenían dexametasona 0,7 µM a 2 µM. Las reacciones de unión se incubaron durante 1 hora a temperatura ambiente y luego se leyó la polarización por fluorescencia en el equipo LJL Analyst ajustado a 550 nm en excitación y 580 nm en emisión, con el espejo dicroico Rodamina 561 instalado. Se determinaron los valores de CI_{50} por ajuste no lineal a una curva de los datos de señal FP a una ecuación logística de 4 variables.

Los compuestos que se encontró se unían al receptor de glucocorticoides se pueden evaluar para determinar la unión al receptor de progesterona (PR), receptor de estrógenos (ER) y receptores de mineralocorticoides (MR) para evaluar la selectividad del compuesto por el GR. Los protocolos para PR y MR son idénticos al procedimiento anterior de GR con las siguientes salvedades: se diluye el lisado de células de insecto PR 1:7,1 y el lisado MR se diluye 1:9,4. La sonda para PR es mifepristona marcada con TAMRA, usada a una concentración final de 5 nM en el ensayo, y los controles negativos (blancos) eran reacciones que contenían mifepristona a 0,7 µM a 2 µM.

El protocolo para ER es similar a los protocolos anteriores pero usa un receptor en el kit Pan Vera, sonda marcada con fluoresceína. Los componentes del ensayo se preparan en los mismos volúmenes que antes, para producir concentraciones finales de ensayo para ER de 15 nM y sonda ES2 de 1 nM. Además, el orden de adición de los componentes se modifica con respecto a los ensayos anteriores: se añade la sonda en primer lugar, seguida por el receptor y el compuesto de ensayo. Las placas se leen en el equipo LJL Analyst ajustado a 485 en excitación y a 530 nm en emisión, con el espejo dicroico de Fluoresceína 505 instalado.

Los compuestos que se encuentra se unen al receptor de glucocorticoides se pueden evaluar para determinar la disociación de la transactivación y transrrepresión por ensayos citados en los Antecedentes de la invención (C.M. Bamberger and H.M. Schulte, Eur. J. Clin. Invest., 2000, 30 (suppl. 3) 6-9) o por los ensayos descritos a continuación.

B. Ensayos celulares del receptor de glucocorticoides

1. Inducción de aromatasa en fibroblastos (Ensayo celular para la transactivación)

La dexametasona, un ligando sintético para el receptor de glucocorticoides (GR) induce la expresión de aromatasa en células de fibroblastos de prepucio humanos. La actividad aromatasa se mide por la conversión de testosterona en estradiol en medios de cultivo. Los compuestos que presentan unión a GR se evalúan para determinar su capacidad para inducir actividad aromatasa en fibroblastos de prepucio humanos.

Se cultivan células de fibroblastos de prepucio humanos (ATCC Nº de catálogo CRL-2429, designación CCD112SK) en placas de 96 pocillos a 50.000 células por pocillo 5 días antes de usar, en medio de Dulbecco modificado por Iscove (GibcoBRL Life Technologies Nº de catálogo 12440-053) suplementado con FBS filtrada en carbón al 10% (Clonetech Nº de catálogo SH30068) y gentamicina (GibcoBRL Life Technologies Nº de catálogo 15710-064). El día del experimento, se reemplaza el medio en los pocillos con medio nuevo. Se tratan las células con compuestos de ensayo hasta concentraciones finales de 10^{-5} M a 10^{-8} M, y testosterona hasta una concentración final de 300 ng/ml. Cada pocillo tiene un volumen total de 100 µl. Las muestras se preparan por duplicado. Los pocillos control incluyen: (a) pocillos que reciben solo testosterona, y (b) pocillos que reciben testosterona más 2 µM de dexametasona para proporcionar una inducción máxima de aromatasa. Las placas se incuban a 37°C durante la noche (15 a 18 horas) y se recogen los sobrenadantes al finalizar la incubación. Se

mide el estradiol en el sobrenadante usando kits ELISA para estradiol (preparados por ALPCO, obtenido de American Laboratory Products N° de catálogo 020-DR-2693) según las instrucciones del fabricante. La cantidad de estradiol es inversamente proporcional a las señales de ELISA en cada pocillo. El grado de inducción de aromatasa por los compuestos de ensayo se expresa como porcentaje con respecto a dexametasona. Los valores de CE_{50} de los compuestos de ensayo se obtienen por ajuste no lineal de la curva.

2. Inhibición de la producción de IL-6 en fibroblastos (Ensayo celular para transrrepresión)

Las células de fibroblastos de prepucio humanos producen IL-6 como respuesta a la estimulación por citoquina IL-1 proinflamatoria. Esta respuesta inflamatoria, medida por la producción de IL-6, se puede inhibir de forma eficaz por dexametasona, un ligando sintético para el receptor de glucocorticoides (GR). Los compuestos que presentan unión a GR se evalúan para determinar su capacidad para inhibir la producción de IL-6 en fibroblastos de prepucio humanos.

Se cultivan células de fibroblasto de prepucio humanos (ATCC N° de catálogo CRL-2429) en placas de 96 pocillos a 5.000 células por pocillo el día antes de su uso en medio de Dulbecco modificado por Iscove (GibcoBRL Life Technologies N° de catálogo 12440-053) suplementado con FBS filtrada en carbón al 10% (Clonetech N° de catálogo SH30068) y Gentamicina (GibcoBRL Life Technologies N° de catálogo 15710-064). Al día siguiente, se reemplaza el medio de los pocillos por medio nuevo. Las células se tratan con IL-1 (rhIL-1α, R&D Systems N° de catálogo 200-LA) hasta una concentración final de 1 ng/ml, y con compuestos de ensayo hasta concentraciones finales de 10^{-5} M a 10^{-8} M, en un volumen total de 200 µl por pocillo. Las muestras se preparan por duplicado. Los pocillos control basales no reciben compuestos de ensayo o IL-1. Los pocillos control positivos reciben solo IL-1 y representan la cantidad máxima (o 100%) de producción de IL-6. Las placas se incuban a 37°C durante la noche (15 a 18 horas) y se recogen los sobrenadantes al final de la incubación. Se determinan los niveles de IL-6 mediante un kit ELISA para IL-6 (MedSystems Diagnostics GmbH, Viena, Austria, N° de catálogo BMS213TEN) de acuerdo con las instrucciones del fabricante. El grado de inhibición de IL-6 por los compuestos de ensayo se expresa como porcentaje con respecto a los controles positivos. Los valores de CI_{50} de los compuestos de ensayo se obtienen por ajuste no lineal a una curva.

La evaluación de la actividad agonista o antagonista de la unión de los compuestos al

receptor de glucocorticoides se puede determinar por cualquiera de los ensayos.

3. Modulación de la inducción de Tirosina Aminotransferasa (TAT) en células de hepatoma de rata

Se ensayan los compuestos para determinar la actividad agonista o antagonista en la inducción de tirosina aminotransferasa (TAT) en células de hepatoma de rata.

Se incubaron células H4-II-E-C3 durante la noche en placas de 96 pocillos (20.000 células/100 µl/pocillo) en medio MEM que contenía FBS inactivado por calor al 10% y aminoácidos no esenciales al 1%. El día siguiente, se estimularon las células con las concentraciones indicadas de dexametasona o compuesto de ensayo (disueltos en DMSO, concentración final de DMSO 0,2%) durante 18 horas. Las células control se trataron con DMSO al 0,2%. Después de 18 horas, las células se lisaron en un tampón que contenía Triton X-100 al 0,1% y se midió la actividad TAT en un ensayo fotométrico usando como sustratos tirosina y alfa-cetoglutarato.

Para medir la actividad antagonista, se preestimularon células de hepatoma mediante adición de dexametasona (intervalos de concentración de 3×10^{-9} M a 3×10^{-8} M) poco antes de aplicar el compuesto de ensayo a las células. Como control se usó mifepristona como antagonista de esteroides no selectivo de GR/PR.

4. Modulación de la inducción de MMTV-Luc en células HeLa

Se ensayan los compuestos para determinar la actividad agonista o antagonista en la estimulación del promotor del MMTV (virus del tumor de mama en el ratón) en células HeLa.

Se transfectaron de forma estable células HeLa con el plásmido pHHLuc que contenía un fragmento de MMTV-LTR (-200 a +100 con respecto al sitio de inicio de la transcripción) clonado delante del gen de la luciferasa (Norden, 1988) y plásmido pcDNA3,1 (Invitrogen) que expresa constitutivamente la resistencia para el antibiótico selectivo GENETICIN®. Se seleccionaron los clones con mejor inducción por el promotor del MMTV y se usaron para los posteriores experimentos.

Se cultivaron las células durante la noche en medio DMEM sin rojo fenol, se suplementaron con CCS (suero de ternero tratado con carbón) al 3% y luego se transfirieron a placas de 96 pocillos (15.000 células /100 µl/pocillo). El día siguiente, se

estimuló la activación del promotor del MMTV mediante la adición de compuesto de ensayo o dexametasona disueltos en DMSO (concentración final 0,2%). Las células control se trataron solo con DMSO. Después de 18 horas, se lisaron las células con reactivo de lisis celular (Promega, N° de catálogo E1531), se añadió reactivo de ensayo de luciferasa (Promega, N° de catálogo E1501) y se midió la luminiscencia usando un luminómetro (BMG, Offenburg).

Para medir la actividad antagonista, se preestimuló el promotor del MMTV añadiendo dexametasona (3×10^{-9} M a 3×10^{-6} M) poco antes de aplicar el compuesto de ensayo a las células. Como control se usó mifepristona como antagonista esteroide no selectivo de GR/PR.

5. Modulación de la producción de IL-8 en células U937

Se ensayan los compuestos para determinar la actividad agonista y antagonista en la inhibición mediada por GR de la secreción de IL-8 inducida por LPS en células U-937.

Se incubaron células U-937 durante 2 a 4 días en medio RPMI1640 que contenía CCS (suero de ternero tratado con carbón) al 10%. Las células se transfectaron a placas de 96 pocillos (40.000 células/100 µl/pocillo) y se estimularon con 1 µg/ml de LPS (disuelto en PBS) en presencia o ausencia de dexametasona o compuesto de ensayo (disuelto en DMSO, concentración final 0,2%). Los pocillos control se trataron con DMSO al 0,2%. Después de 18 horas, se midió por ELISA la concentración de IL-8 en el sobrenadante celular usando el equipo "OptEIA para IL-8 humana" (Pharmingen, N° de catálogo 2654KI).

Para medir la actividad antagonista, se inhibió la secreción de IL-8 inducida por LPS añadiendo dexametasona (3×10^{-9} M a 3×10^{-8} M) poco antes de aplicar el compuesto de ensayo a las células. Como control se usó mifepristona como antagonista esteroide no selectiva de GR/PR.

6. Modulación de la expresión de ICAM-Luc en células HeLa

Se ensayan los compuestos para determinar la actividad agonista o antagonista de la activación del promotor de ICAM inducida por TNF-alfa en células HeLa.

Se cotransfectaron de forma estable células HeLa con un plásmido que contenía un fragmento de 1,3 kb del promotor de ICAM humano (-1353 a -9 con respecto al sitio de inicio de la transcripción, Ledebur and Parks, 1995) clonado delante del gen de la

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luciferasa y plásmido pcDNA3,1 (Invitrogen) que expresó constitutivamente el gen de la resistencia al antibiótico GENETICIN®. Se seleccionaron los clones con mejor inducción del promotor de ICAM y se usaron para los posteriores experimentos. Las células se transfectaron a placas de 96 pocillos (15,000 células/100 µl/pocillo) en medio DMEM suplementado con CCS al 3%. El día siguiente se indujo la activación del promotor de ICAM mediante adición de 10 ng/ml de TNF-alfa recombinante (R&D System, N° de catálogo 210-TA). De forma simultánea, se trataron las células con el compuesto de ensayo o dexametasona (disueltos en DMSO, concentración final 0,2%). Las células control se trataron solo con DMSO. Después de 18 horas, se lisaron las células con reactivo de lisis celular (Promega, N° de catálogo E1531), se añadió reactivo de ensayo de liciferasa (Promega, N° de catálogo E1501) y se midió la luminiscencia por incandescencia usando un luminómetro (BMG, Offenburg).

Para medir la actividad antagonista, se inhibió la activación del promotor de ICAM inducida por TNF-alfa añadiendo dexametasona (3×10^{-9} M a 3×10^{-8} M) poco antes de aplicar el compuesto de ensayo a las células. Como control se usó mifepristona como antagonista esteroide no selectivo de GR/PR.

En general, el intervalo de potencia preferido en los anteriores ensayos varía de 0,1 nM a 10 µM, el intervalo de potencia más preferido es 0,1 nM a 1 µM, y el intervalo de potencia más preferido es 0,1 nM a 100 nM.

Los compuestos representativos de la invención se han ensayado y han mostrado actividad como moduladores de la función del receptor de glucocorticoides en uno o más de los anteriores ensayos. Por ejemplo, los siguientes compuestos de la invención de Fórmula (IA) han demostrado una potente actividad en el ensayo de unión a GR:

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

2-(2,6-Dicloropiridin-4-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

2-[3-(2,6-Dicloropiridin-4-ilmetil)-4,4,4-trifluoro-3-hidroxi-1,1-dimetilbutil]-4-fluorofenol;

4-(5-Bromo-2,3-dihidrobenzofuran-7-il)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

2-(1*H*-Bencimidazol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorofenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(quinolin-4-ilmetil)pentan-2-ol;

4-(2,3-dihidro-5-cianobenzofuran-7-il)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(2-cloropiridin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-hidroxifenil)-4-metil-2-(2-cloropiridin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(2-cloroquinolin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-hidroxifenil)-4-metil-2-(2-cloroquinolin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-(4-metoxifenil)-4-metilpentan-2-ol;

4-[4,4,4-Trifluoro-3-hidroxi-3-(1*H*-indol-2-ilmetil)-1,1-dimetilbutil]fenol;

1,1,1-Trifluoro-2-(5-fluoro-1*H*-indol-2-ilmetil)-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

4-(2,3-dihidrobenzofuran-7-il)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(2-bromopiridin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(7-metil-1*H*-benzoimidazol-2-ilmetil)pentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(4-metil-1*H*-indol-2-ilmetil)butil]fenol;

4-Fluoro-2-[4,4,4-trifluoro-3-(7-fluoro-1*H*-indol-2-ilmetil)-3-hidroxi-1,1-dimetilbutil]fenol;

1,1,1-Trifluoro-2-(6-fluoro-1*H*-benzoimidazol-2-ilmetil)-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

2-(6,7-Difluoro-1*H*-benzoimidazol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(5-Bromo-2,3-dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(3-Etil-2-metoxifenil)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

2-Etil-6-(4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

2-Etil-6-[4,4,4-trifluoro-3-hidroxi-3-(1*H*-indol-2-ilmetil)-1,1-dimetilbutil]fenol;

2-(5,7-Dimetil-1*H*-benzoimidazol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

2-[3-(5,7-Dimetil-1*H*-benzoimidazol-2-ilmetil)-4,4,4-trifluoro-3-hidroxi-1,1-dimetilbutil]-4-fluorofenol;

1,1,1-Trifluoro-4-(3-metoxifenil)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-(3-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-4-metil-2-(4-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorofenil)-4-metil-2-(4-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorofenil)-4-metil-2-(4-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-metil-2-quinolin-4-ilmetil-4-(3-trifluorometilfenil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-4-metil-2-(7-metil-1*H*-benzoimidazol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-(3-trifluorometilfenil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

5-Fluoro-2-(4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

4-(5-Bromo-4-fluoro-2-metoxifenil)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

2-(2-Fenil-4-metilimidazol-1-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihidrobenzofuran-7-il)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

2-(2-Fenilimidazol-1-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihidrobenzofuran-7-il)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-metil-4-(5-metil-2,3-dihidrobenzofuran-7-il)-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-fenilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-(5-metil-2,3-dihidrobenzofuran-7-il)pentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-*m*-tolilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-naftalen-2-ilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-*o*-tolilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-*p*-tolilpentan-2-ol;

4-(2,3-Dihidrobenzofuran-5-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(7-Bromo-2,3-dihidrobenzofuran-5-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(2,3-Dihidrobenzofuran-5-il)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(1-metoxinaftalen-2-il)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

2-(4,4,4-Trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)naftalen-1-ol;

1,1,1-Trifluoro-4-metil-4-naftalen-2-il-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-(1-metoxinaftalen-2-il)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-metil-2-quinolin-4-ilmetil-4-*p*-tolilpentan-2-ol;

4-Croman-8-il-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-4-metil-4-fenil-2-quinolin-4-ilmetilpentan-2-ol;

4-(6-Bromocroman-8-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[3,2-*b*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[2,3-*b*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorofenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-metil-4-fenil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-(7-fluoroquinolin-4-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorofenil)-2-(7-fluoroquinolin-4-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorofenil)-2-(5-fluoroquinolin-4-ilmetil)-4-metilpentan-2-ol;

2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

2-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

2-[4-(5-Fluoro-2-metilfenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

1,1,1-Trifluoro-4-(2-metoxifenil)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-(2-metoxifenil)-4-metilpentan-2-ol;

2-[4-(5-Fluoro-2,3-dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

4-(5-Bromo-2-metoxifenil)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(5-Bromo-2-metoxifenil)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

2-(4,4,4-Trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

1,1,1-Trifluoro-4-metil-4-fenil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

2-[4-(5-Bromo-2,3-dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

4-Bromo-2-(4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

1,1,1-Trifluoro-4-(4-fluorofenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

2-[4-(4-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometil-pentil]-1*H*-indol-3-carbonitrilo;

2-(2-Hidroxi-4-metil-4-fenil-2-trifluorometilpentil)-4-metil-1*H*-indol-6-carbonitrilo;

2-[4-(3-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

2-[4-(4-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

2-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-metil-4-fenil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

2-(2-Hidroxi-4-metil-4-fenil-2-trifluorometilpentil)-1*H*-indol-5-carbonitrilo;

2-[4-(3-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

2-[4-(4-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-(5,6,7,8-tetrahidroquinolin-4-ilmetil)pentan-2-ol;

1-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

2-(2-Hidroxi-4-metil-4-fenil-2-trifluorometilpentil)-1*H*-indol-3-carbonitrilo;

5-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)butil]fenol;

2-[4-(4-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

2-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

2-[4-(3-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

2-[4-(4-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

2-[4-(5-Fluoro-2-metilfenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)butil]fenol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-metil-4-fenilpentan-2-ol;

Éster metílico del ácido 2-[4-(4-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carboxílico;

1-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(3-metil-1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(3-metoxifenil)-4-metil-2-(5-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol;

2-[2-Hidroxi-4-(3-metoxifenil)-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)butil]fenol;

5-Fluoro-2-[4,4,4-trifluoro-3-(7-fluoro-1*H*-indol-2-ilmetil)-3-hidroxi-1,1-dimetilbutil]fenol;

2-[4-(5-Fluoro-2-hidroxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(3-metil-1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)butil]fenol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-tiofen-3-ilpentan-2-ol;

1,1,1-Trifluoro-4-metil-2-quinolin-4-ilmetil-4-tiofen-3-ilpentan-2-ol;

5-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)butil]fenol;

1,1,1-Trifluoro-4-(3-fluorofenil)-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

3-(4,4,4-Trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

Éster metílico del ácido 2-[4-(5-bromo-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carboxílico;

Éster metílico del ácido 2-[4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carboxílico;

4-(2,6-Dimetilfenil)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

3-[4,4,4-Trifluoro-3-hidroxi-3-(1*H*-indol-2-ilmetil)-1,1-dimetilbutil]fenol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihidrobenzofuran-7-il)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

2-[2-Hidroxi-4-(3-metoxifenil)-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo; y

2-[4-(5-Bromo-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo.

Los siguientes compuestos de la invención de Fórmula (IB) han demostrado una potente actividad en el ensayo de unión a GR:

5-(5-Fluoro-2-metoxifenil)-3-(bencimidazol-2-ilmetil)-2,2,5-trimetilhexan-3-ol;

4-(5-Fluoro-2-metoxifenil)-1-fluoro-2-(indol-2-ilmetil)-4-metilpentan-3-ol;

1-Ciclopropil-4-(5-fluoro-2-metoxifenil)-2-(indol-2-ilmetil)-4-metilpentan-2-ol;

5-(5-Fluoro-2-metoxifenil)-3-(indol-2-ilmetil)-2,5-dimetilhexan-3-ol;

5-(5-Fluoro-2-metoxifenil)-3-(indol-2-ilmetil)-5-metilhexan-3-ol; y

2-Ciclopropil-4-(5-fluoro-2-metoxifenil)-4-metil-1-(1*H*-pirrolo[2,3-*c*]piridin-2-il)pentan-2-ol.

Además, se han ensayado los siguientes compuestos de la invención de Fórmula (IA) y han mostrado actividad como potentes agonistas de la función del receptor de glucocorticoides en uno o más de los ensayos anteriores:

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

2-(2,6-Dicloropiridin-4-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

4-(5-Bromo-2,3-dihidrobenzofuran-7-il)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

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1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(quinolin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

4-(2,3-dihidrobenzofuran-7-il)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(4-metil-1*H*-indol-2-ilmetil)butil]fenol;

4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(5-Bromo-2,3-dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

2-[3-(5,7-Dimetil-1*H*-benzoimidazol-2-ilmetil)-4,4,4-trifluoro-3-hidroxi-1,1-dimetilbutil]-4-fluorofenol;

1,1,1-Trifluoro-4-(3-metoxifenil)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-(3-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-4-metil-2-(4-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorofenil)-4-metil-2-(4-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorofenil)-4-metil-2-(4-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-metil-2-quinolin-4-ilmetil-4-(3-trifluorometilfenil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-(3-trifluorometilfenil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

5-Fluoro-2-(4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

4-(5-Bromo-4-fluoro-2-metoxifenil)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihidrobenzofuran-7-il)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihidrobenzofuran-7-il)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-metil-4-(5-metil-2,3-dihidrobenzofuran-7-il)-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-(5-metil-2,3-dihidrobenzofuran-7-il)pentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-*m*-tolilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-*o*-tolilpentan-2-ol;

4-(7-Bromo-2,3-dihidrobenzofuran-5-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

1,1,1-Trifluoro-4-metil-4-fenil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-(7-fluoroquinolin-4-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorofenil)-2-(5-fluoroquinolin-4-ilmetil)-4-metilpentan-2-ol;

2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

2-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

2-[4-(5-Fluoro-2-metilfenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

1,1,1-Trifluoro-4-(2-metoxifenil)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-(2-metoxifenil)-4-metilpentan-2-ol;

2-[4-(5-Fluoro-2,3-dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

4-(5-Bromo-2-metoxifenil)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(5-Bromo-2-metoxifenil)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

2-(4,4,4-Trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

1,1,1-Trifluoro-4-metil-4-fenil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

2-[4-(5-Bromo-2,3-dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

4-Bromo-2-(4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-

ilmetil)pentan-2-ol;

2-[4-(4-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometil-pentil]-1*H*-indol-3-carbonitrilo;

2-(2-Hidroxi-4-metil-4-fenil-2-trifluorometilpentil)-4-metil-1*H*-indol-6-carbonitrilo;

2-[4-(3-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

2-[4-(4-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

2-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-metil-4-fenil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

2-(2-Hidroxi-4-metil-4-fenil-2-trifluorometilpentil)-1*H*-indol-5-carbonitrilo;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-(5,6,7,8-tetrahidroquinolin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

5-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)butil]fenol;

2-[4-(4-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

2-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

2-[4-(4-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

2-[4-(5-Fluoro-2-metilfenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)butil]fenol;

1-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)butil]fenol;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(3-metil-1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

2-[4-(5-Fluoro-2-hidroxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;
2-[2-Hidroxi-4-(3-metoxifenil)-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo; y

2-[4-(5-Bromo-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo.

Se han ensayado los siguientes compuestos de Fórmula (IB) y han mostrado actividad como agonistas de la función del receptor de glucocorticoides en uno o más de los ensayos anteriores:

2-Ciclopropil-4-(5-fluoro-2-metoxifenil)-1-(1*H*-indol-2-il)-4-metilpentan-2-ol; y

2-Ciclopropil-4-(5-fluoro-2-metoxifenil)-4-metil-1-(1*H*-pirrolo[2,3-*c*]piridin-2-il)pentan-2-ol.

La invención también proporciona procedimientos para modular la función del receptor de glucocorticoides en un paciente que comprende administrar al paciente un compuesto conforme a la invención. Si el propósito de modular la función del receptor de glucocorticoides en un paciente es tratar un estado de enfermedad o trastorno, la administración comprende preferiblemente una cantidad terapéutica o farmacéuticamente eficaz de un compuesto farmacéuticamente aceptable conforme a la invención. Si el propósito de modular la función del receptor de glucocorticoides en un paciente es para fines de diagnóstico u otros fines (por ejemplo, determinar la idoneidad del paciente para la terapia o la sensibilidad a diversas subdosis terapéuticas de los compuestos conforme a la invención), la administración comprende preferiblemente una cantidad eficaz de un compuesto conforme a la invención, es decir, la cantidad necesaria para obtener el efecto o grado de modulación deseado.

Procedimientos de uso terapéutico

Como se ha expuesto antes, los compuestos de la invención son útiles para modular la función del receptor de glucocorticoides. Al hacerlo, estos compuestos tienen uso terapéutico en el tratamiento de estados de enfermedad y trastornos mediados por la función del receptor de glucocorticoides o que se beneficiarían de modulación de la función del receptor de glucocorticoides.

Puesto que los compuestos de la invención modulan la función del receptor de glucocorticoides, tienen actividad antiinflamatoria y antialérgica, inmunosupresora y antiproliferativa muy útil y pueden usarse en pacientes como fármacos, en particular en forma de composiciones farmacéuticas como las mostradas a continuación, para el tratamiento de estados de enfermedad y trastornos.

Los compuestos agonistas conforme a la invención se pueden usar en pacientes como fármacos para el tratamiento de los siguientes estados de enfermedad o indicaciones que se llevan a cabo por procesos inflamatorios, alérgicos y/o proliferativos:

(i) Enfermedades pulmonares: enfermedades pulmonares obstructivas, crónicas de cualquier génesis, en particular asma bronquial y enfermedad pulmonar obstructiva crónica (EPOC); síndrome de dificultad respiratoria en el adulto

(SDRA); bronquiectasias; bronquitis de diversas génesis; todas las formas de enfermedades pulmonares restrictivas, en particular alveolitis alérgica; todas las formas de edema pulmonar, en particular edema pulmonar tóxico; todas las formas de enfermedades pulmonares intersticiales de cualquier génesis, por ejemplo, pneumonitis por radiación; y sarcoidosis y granulomatosis, en particular, enfermedad de Boeck;

(ii) Enfermedades reumáticas o enfermedades autoinmunes o enfermedades de las articulaciones: todas las formas de enfermedades reumáticas, especialmente artritis reumatoide, fiebre reumática aguda y polimialgia reumática; artritis reactiva; enfermedades reumáticas de los tejidos blandos; enfermedades inflamatorias de los tejidos blandos de otra génesis; síntomas artríticos en enfermedades degenerativas de las articulaciones (artrosis); artritis traumática; colagenosis de cualquier génesis, por ejemplo, lupus eritematoso sistémico, esclerodermia, polimiositis, dermatomiositis, síndrome de Sjögren, enfermedad de Still y síndrome de Felty;

(iii) Enfermedades alérgicas: todas las formas de reacciones alérgicas, por ejemplo, edema angioneurótico, fiebre del heno, picaduras de insectos, reacciones alérgicas a fármacos, derivados de la sangre, agentes de contraste y similares, shock anafiláctico (anafilaxis), urticaria, edema angioneurótico y dermatitis por contacto;

(iv) Enfermedades por vasculitis: panarteritis nudosa, poliarteritis nudosa, arteritis temporal, granulomatosis de Wegner, artritis de células gigantes y eritema nudoso;

(v) Enfermedades dermatológicas: dermatitis atópica, en particular en niños; psoriasis; pitiriasis rubra pilaris; enfermedades eritematosas desencadenadas por diversos agentes nocivos, por ejemplo, radiación, agentes químicos, quemaduras y similares; dermatosis ampollosa; enfermedades del complejo liquenoide; prurito (por ejemplo, de génesis alérgica); dermatosis seborreica; rosácea; pénfingo vulgar; eritema multiforme exudativo; balanitis; vulvitis; pérdida de cabello tal como la encontrada en alopecia aereata; y linfomas cutáneos por linfocitos T;

(vi) Enfermedades renales; síndrome nefrótico; y todos los tipos de nefritis, por ejemplo, glomerulonefritis;

(vii) Enfermedades hepáticas: disgregación aguda de células del hígado; hepatitis aguda de diversas génesis, por ejemplo, viral, tóxica, inducida por fármacos; y hepatitis agresiva y/o crónicamente intermitente;

(viii) Enfermedades gastrointestinales: enfermedades inflamatorias del intestino, por

ejemplo, enteritis regional (enfermedad de Crohn), colitis ulcerosa; gastritis; esofagitis péptica (esofagitis por reflujo); y gastroenteritis de otra génesis, por ejemplo, esprué no tropical;

(ix) Enfermedades proctológicas: eccema anal; fisuras; hemorroides; y proctitis idiopática;

(x) Enfermedades de los ojos: queratitis alérgica, uveitis o iritis; conjuntivitis; blefaritis; neuritis del nervio óptico; coroiditis; y oftalmia simpática;

(xi) Enfermedades del área del oído, nariz y garganta (ORL): rinitis alérgica o fiebre del heno; otitis externa, por ejemplo, causada por eccema por contacto, infección o similar; y otitis media;

(xii) Enfermedades neurológicas: edema cerebral; esclerosis múltiple; encefalomielitis aguda; meningitis; lesión aguda de la médula espinal; apoplejía; y diversas formas de convulsiones, por ejemplo, espasmos con movimientos oscilatorios de cabeza;

(xiii) Enfermedades de la sangre: anemia hemolítica adquirida; y trombocitopenia idiopática;

(xiv) Enfermedades tumorales: leucemia linfática aguda; linfoma maligno; linfogranulomatosis; linfosarcoma; metástasis extensiva, en particular en carcinoma de mama, bronquial y de próstata;

(xv) Enfermedades endocrinas; oftalmopatía endocrina; orbitopatía endocrina; crisis tirotóxica; tiroiditis de Quervain; tiroiditis de Hashimoto; Morbus Basedow; tiroiditis granulomatosa; estruma linfomatosa; y enfermedad de Grave;

(xvi) Enfermedades de trasplantes de órganos y tejidos y del injerto frente al huésped;

(xvii) Estados severos de shock, por ejemplo, shock séptico, shock anafiláctico y síndrome de respuesta inflamatoria sistémica (SRIS);

(xviii) Terapia de sustitución en: insuficiencia suprarrenal primaria congénita, por ejemplo, síndrome adrenogenital; insuficiencia suprarrenal primaria adquirida, por ejemplo, enfermedad de Addison, adrenalitis autoinmune, posinfección, tumores, metástasis, etc.; insuficiencia suprarrenal secundaria congénita, por ejemplo, hipopituitarismo congénito; e insuficiencia suprarrenal secundaria adquirida, por ejemplo, posinfección, tumores, metástasis, etc.;

(xix) Dolor de génesis inflamatoria, por ejemplo, lumbalgia; y

(xx) Otros estados de enfermedad o trastornos diversos incluyendo diabetes tipo I diabetes dependiente de insulina), osteoartritis, síndrome de Guillian-Barre, restenosis después de una angioplastia coronaria percutánea transluminal, enfermedad de Alzheimer, dolor crónico y agudo, aterosclerosis, lesión por reperfusión, enfermedades de resorción ósea, insuficiencia cardíaca congestiva,

infarto de miocardio, lesión térmica, lesión en varios órganos secundaria a traumatismo, meningitis purulenta aguda, enterocolitis necrotizante y síndromes asociados con hemodiálisis, leucoféresis y transfusión de granulocitos.

Además, los compuestos conforme a la invención se pueden usar para el tratamiento de cualquier otro estado de enfermedad o trastorno no citado antes que se haya tratado, se trate o se vaya a tratar con glucocorticoides sintéticos (véase por ejemplo, H.J. Hatz, Glucocorticoide: Immunologische Grundlagen, Pharmakologie und Therapierichtlinien [Glucocorticoids: Immunological Fundamentals, Pharmacology, and Therapeutic Guidelines], Stuttgart: Verlagsgesellschaft mbH, 1998, que se incorpora en la presente memoria como referencia en su totalidad). La mayoría o todas las indicaciones (i) a (xx) citadas antes se describen con detalle en H.J. Hatz, Glucocorticoide: Immunologische Grundlagen, Pharmakologie und Therapierichtlinien. Por otro lado, los compuestos de la invención también se pueden usar para tratar trastornos distintos a los listados antes o citados o descritos en la presente memoria, incluyendo los Antecedentes de la Invención.

Los compuestos antagonistas conforme a la invención, ya sean antagonistas totales o antagonistas parciales, se pueden usar en pacientes como fármacos para el tratamiento de los siguientes estados de enfermedad o indicaciones sin quedar limitados a los mismos: diabetes tipo II (diabetes no dependiente de insulina); obesidad; enfermedades cardiovasculares; hipertensión; arteriosclerosis; enfermedades neurológicas, tales como psicosis y depresión; tumores suprarrenales y pituitarios; glaucoma; y síndrome de Cushing basado en un tumor que segregue ACTH como adenoma pituitario. En particular, los compuestos de la invención son útiles para tratar obesidad y todos los estados de enfermedad e indicaciones relacionadas con el metabolismo mal regulado de los ácidos grasos como hipertensión, aterosclerosis y otras enfermedades cardiovasculares. Usando los compuestos de la invención que son antagonistas del GR será posible obtener un efecto antagónico del metabolismo de los hidratos de carbono y del metabolismo de los ácidos grasos. Así, los compuestos antagonistas de la invención son útiles en el tratamiento de todos los estados de enfermedad y trastornos que implican un metabolismo aumentado de los hidratos de carbono, proteínas y lípidos e incluirán estados de enfermedad y trastornos que conducen a catabolismo como debilidad muscular (como un ejemplo de metabolismo de las proteínas).

Procedimientos de uso diagnóstico

Los compuestos de la invención se pueden usar también en aplicaciones de diagnóstico

y para fines comerciales y de otro tipo como patrones en ensayos de unión competitiva. En tales usos, los compuestos de la invención se pueden usar en forma de los propios compuestos o pueden modificarse uniéndolos a radioisótopos, marcadores luminiscentes o fluorescentes o similares, con el fin de obtener una sonda con radioisótopos, luminiscente o fluorescente, como será bien conocido por los expertos en la técnica y se describe en Handbook de Fluorescent Probes and Research Chemicals, 6ª Edición, R.P. Haugland (ed.), Eugene: Molecular Probes, 1996; Fluorescence and Luminescence Probes for Biological Activity, W.T. Mason (ed.), San Diego: Academic Press, 1993; Receptor-Ligand Interaction. A Practical Approach, E.C. Hulme (ed.), Oxford: IRL Press, 1992, cada una de las cuales se incorpora en la presente memoria como referencia en su totalidad.

Administración general y composiciones farmacéuticas

Cuando se usan como medicamentos, los compuestos de la invención se administran típicamente en forma de una composición farmacéutica. Tales composiciones se pueden preparar usando procedimientos bien conocidos en la técnica farmacéutica y comprenden al menos un compuesto de la invención. Los compuestos de la invención se pueden administrar también solos o combinados con adyuvantes que mejoran la estabilidad de los compuestos de la invención, facilitan la administración de composiciones farmacéuticas que los contienen en ciertas realizaciones, proporcionan una mayor disolución o dispersión, una mayor actividad inhibidora, proporcionan terapias auxiliares y similares. Los compuestos conforme a la invención se pueden usar por si solos o combinados con otras sustancias activas conforme a la invención, opcionalmente también combinados con otras sustancias farmacológicamente activas. En general, los compuestos de esta invención se administran en una cantidad terapéutica o farmacéuticamente eficaz, aunque se pueden administrar en menores cantidades con fines de diagnóstico o de otro tipo.

En particular, los compuestos de la invención son útiles en combinación con glucocorticoides o corticosteroides. Como se ha explicado antes, la terapia convencional para una diversidad de trastornos inmunes e inflamatorios incluye la administración de corticosteroides, que tienen la capacidad de suprimir las respuestas inmunológicas e inflamatorias. (A.P. Truhan *et al.*, Annals of Allergy, 1989, 62, páginas 375-391; J.D. Baxter, Hospital Practice, 1992, 27, páginas 111-134; R.P. Kimberly, Curr. Opin. Rheumatol., 1992, 4, páginas 325-331; M.H. Weisman, Curr. Opin. Rheumatol., 1995, 7, páginas 183-190; W. Sterry, Arch. Dermatol. Res., 1992, 284 (Suppl.), páginas S27-S29). Sin embargo, aunque terapéuticamente beneficioso, el uso de corticosteroides se

asocia con una serie de efectos secundarios, que varían de leves a posiblemente mortales, en especial con uso de esteroides prolongado y/o en altas dosis. Por consiguiente, serían muy deseables para evitar efectos secundarios indeseados procedimientos y composiciones que permitan el uso de una dosis eficaz menor de corticosteroides (denominado "efecto ahorrador de esteroides"). Los compuestos de la invención proporcionan dicho efecto ahorrador de esteroides alcanzando el efecto terapéutico deseado y permitiendo al mismo tiempo el uso de menores dosis y administración menos frecuente de glucocorticoides y corticosteroides.

La administración de los compuestos de la invención, en forma pura o en una composición farmacéutica apropiada, se puede llevar a cabo usando cualquiera de los modos aceptados de administración de composiciones farmacéuticas. Así, la administración puede realizarse, por ejemplo, por vía oral, bucal (por ejemplo sublingual), nasal, parenteral, tópica, transdérmica, vaginal o rectal en formas de dosificación sólidas, semisólidas, en polvo liofilizado o líquidas, tales como por ejemplo comprimidos, supositorios, pastillas, cápsulas de gelatina dura y blanda elásticas, polvos, soluciones, suspensiones o aerosoles, o similares, con preferencia en formas de dosis unitaria adecuadas para la administración sencilla de dosis precisas. Las composiciones farmacéuticas incluirán por lo general un vehículo o excipiente farmacéutico convencional y un compuesto de la invención como el/un agente activo y, además, pueden incluir otros agentes medicinales, agentes farmacéuticos, excipientes, adyuvantes, diluyentes, vehículos o combinaciones de los mismos. Tales excipientes, vehículos o aditivos farmacéuticamente aceptables, así como los métodos de preparación de las composiciones farmacéuticas para diversos modos de administración son bien conocidos por los expertos en la técnica. El estado de la técnica se presenta, por ejemplo, en Remington: The Science and Practice of Pharmacy, 20ª Edición, A. Gennaro (ed.), Lippincott Williams & Wilkins, 2000; Handbook of Pharmaceutical Additives, Michael & Irene Ash (eds.), Gower, 1995; Handbook of Pharmaceutical Excipients, A.H. Kibbe (ed.), American Pharmaceutical Ass'n, 2000; H.C. Ansel and N.G. Popovish, Pharmaceutical Dosage Forms and Drug Delivery Systems, 5ª ed., Lea and Febiger, 1990; cada uno de los cuales se incorpora en la presente memoria como referencia en su totalidad para describir mejor el estado de la técnica.

Como esperará un experto en la técnica, las formas de los compuestos de la invención usadas en una formulación farmacéutica particular se seleccionarán (por ejemplo, sales) de modo que posean características físicas adecuadas (por ejemplo solubilidad en agua), que sean requeridas para que la formulación sea eficaz.

Composiciones farmacéuticas adecuadas para administración bucal (sublingual) incluyen tabletas que comprenden un compuesto de la presente invención en una base aromatizada, normalmente sacarosa y goma arábiga o tragacanto, y pastillas que comprenden el compuesto en una base inerte como gelatina y glicerina o sacarosa o goma arábiga.

Composiciones farmacéuticas adecuadas para administración parenteral comprenden preparaciones acuosas estériles de un compuesto de la presente invención. Estas preparaciones se administran preferiblemente por vía intravenosa, aunque también se puede efectuar la administración por medio de inyección subcutánea, intramuscular o intradérmica. Se usan corrientemente formulaciones farmacéuticas inyectables basadas en solución salina estéril inyectable, solución salina tamponada con fosfato, suspensiones oleaginosas u otros vehículos inyectables conocidos en la técnica y que generalmente proporcionan una solución o suspensión inyectable estéril en un diluyente o disolvente parenteralmente aceptable no tóxico, incluyendo 1,3-butanodiol, agua, solución de Ringer, solución de cloruro sódico isotónica, aceites fijos como mono o diglicéridos sintéticos, ácidos grasos como ácido oleico y similares. Tales formulaciones farmacéuticas inyectables se formulan conforme a la técnica conocida usando agentes de dispersión o de sedimentación adecuados y agentes de suspensión. Las composiciones inyectables contendrán por lo general 0,1 a 5% p/p de un compuesto de la invención.

Las formas de dosificación sólidas para administración oral de los compuestos incluyen cápsulas, comprimidos, píldoras, polvos y gránulos. Para dicha administración oral, se forma una composición farmacéuticamente aceptable que contiene un compuesto(s) de la invención mediante la incorporación de cualquiera de los excipientes empleados normalmente, tales como por ejemplo, calidades farmacéuticas de manitol, lactosa, almidón, almidón pregelatinizado, estearato de magnesio, sacarina sódica, talco, derivados éter de la celulosa, glucosa, gelatina, sacarosa, citrato, propilgalato y similares. Tales formulaciones farmacéuticas sólidas pueden incluir formulaciones, como son bien conocidas en la técnica, para proporcionar una liberación prolongada o sostenida del fármaco al tracto gastrointestinal por una serie de mecanismos, que incluyen, aunque no quedan limitados a los mismos, liberación sensible al pH desde la forma de dosificación basada en un pH cambiante del intestino delgado, erosión lenta de un comprimido o cápsula, retención en el estómago en base a propiedades físicas de la formulación, bioadhesión de la forma de dosificación a la capa superficial de la

membrana mucosa del tracto intestinal, o liberación enzimática del fármaco activo desde la forma de dosificación.

Las formas de dosificación líquidas para administración oral de los compuestos incluyen emulsiones, microemulsiones, soluciones, suspensiones, jarabes y elixires, conteniendo opcionalmente adyuvantes farmacéuticos en un vehículo, tal como por ejemplo, agua, solución salina, dextrosa acuosa, glicerol, etanol y similares. Estas composiciones también pueden contener otros adyuvantes como agentes humectantes, emulsionantes, de suspensión, edulcorantes, aromatizantes y perfumantes.

Las formas de dosificación tópica de los compuestos incluyen pomadas, pomadas espesas, cremas, lociones, geles, polvos, soluciones, pulverizadores, inhaladores, pomadas oculares, gotas para ojos y oídos, apósitos impregnados y aerosoles, y pueden contener aditivos convencionales apropiados tales como conservantes, disolventes para ayudar a penetrar al fármaco y emolientes en pomadas y cremas. La aplicación tópica puede realizarse una vez o más de una vez al día dependiendo de las consideraciones médicas habituales. Además, los compuestos preferidos para la presente invención se pueden administrar en forma intranasal a través de uso tópico de vehículos intranasales adecuados. Las formulaciones también pueden contener vehículos compatibles convencionales, tales como bases de cremas o pomadas y etanol o alcohol oleílico para lociones. Tales vehículos pueden estar presentes de aproximadamente 1% hasta aproximadamente 98% de la formulación, más normalmente constituirán hasta aproximadamente 80% de la formulación.

También es posible la administración transdérmica. Las composiciones farmacéuticas adecuadas para administración transdérmica pueden presentarse como parches discretos adaptados para permanecer en contacto íntimo con la epidermis del receptor durante un período prolongado de tiempo. Para administrase en forma de sistema de liberación transdérmico, la administración de la dosis será naturalmente continua y no intermitente durante la pauta de dosificación. Tales parches contienen adecuadamente un compuesto de la invención en una solución acuosa opcionalmente tamponada, disuelto y/o dispersado en un adhesivo, o dispersado en un polímero. Una concentración adecuada del compuesto activo varía de aproximadamente 1% a 25%, preferiblemente aproximadamente 3% a 15%.

Para administración por inhalación, los compuestos de la invención se liberan convenientemente en forma de un pulverizador de aerosol desde un dispositivo de

pulverización dotado de una bomba que no requiere un gas propulsor o desde un envase a presión o un nebulizador con el uso de un propulsor adecuado, por ejemplo, diclorodifluormetano, triclorofluormetano, diclorotetrafluoretano, tetrafluoretano, heptafluoretano, dióxido de carbono u otro gas adecuado. En cualquier caso, la unidad de dosis del pulverizador de aerosol se puede determinar disponiendo una válvula para liberar una cantidad medida de modo que el inhalador de dosis medida resultante (IDM) se usa para administrar los compuestos de la invención de una forma reproducible y controlada. Dichos dispositivos inhaladores, nebulizadores o atomizadores se conocen en la técnica anterior, por ejemplo, en las publicaciones internacionales PCT números WO 97/12687 (en particular su Figura 6, que es la base del nebulizador comercial RESPIMAT®); WO 94/07607; WO 97/12683; y WO 97/20590, a las que se hace referencia en la presente memoria y cada una de las cuales se incorpora en la presente memoria como referencia en su totalidad.

La administración rectal se puede efectuar usando supositorios de dosis unitaria en los que el compuesto se mezcla con sólidos de bajo punto de fusión solubles en agua o insolubles en agua tales como grasas, manteca de cacao, gelatina glicerada, aceites vegetales hidrogenados, mezclas de polietilenglicoles de diversos pesos moleculares, o ésteres de ácidos grasos de polietilenglicoles, o similares. Normalmente el compuesto activo es el componente minoritario, con frecuencia de aproximadamente 0,05 a 10% en peso, siendo el resto el componente base.

En todas las composiciones farmacéuticas anteriores, los compuestos de la invención se formulan con un vehículo o excipiente aceptable. Naturalmente, los vehículos o excipientes usados deberán ser aceptables en el sentido de que sean compatibles con el resto de ingredientes de la composición y no serán perjudiciales para el paciente. El vehículo o excipiente puede ser un sólido o líquido o ambos, y preferiblemente se formula con el compuesto de la invención como una composición de dosis unitaria, por ejemplo, como un comprimido, que puede contener de 0,05% a 95% en peso del compuesto activo. Tales vehículo o excipientes incluyen cargas inertes o diluyentes, ligantes, lubricantes, agentes disgregantes, retardadores de la solución, aceleradores de resorción, agentes absorbentes y agentes colorantes. Los ligantes adecuados incluyen almidón, gelatina, azúcares naturales como glucosa o β-galactosa, edulcorantes de maíz, gomas naturales y sintéticas como goma arábiga, tragacanto o alginato sódico, carboximetilcelulosa, polietilenglicol, ceras y similares. Los lubricantes incluyen oleato sódico, estearato sódico, estearato de magnesio, benzoato sódico, acetato sódico, cloruro sódico y similares. Los disgregantes incluyen almidón, metilcelulosa, agar, bentonita,

goma xantana y similares.

Por lo general, una dosis diaria terapéuticamente eficaz varía de aproximadamente 0,001 mg a aproximadamente 15 mg/kg de peso corporal por día de un compuesto de la invención; con preferencia, de aproximadamente 0,1 mg a aproximadamente 10 mg/kg de peso corporal por día; y, lo más preferible, de aproximadamente 0,1 mg a aproximadamente 1,5 mg/kg de peso corporal por día. For ejemplo, para administración a una persona de 70 kg, el intervalo de dosis variará de aproximadamente 0,07 mg a aproximadamente 1050 mg por día de un compuesto de la invención, preferiblemente, de aproximadamente 7,0 mg a aproximadamente 700 mg por día y, lo más preferible, de aproximadamente 7,0 mg a aproximadamente 105 mg por día. Para determinar un nivel y pauta de dosificación óptima puede ser necesario cierto grado de optimización de dosis rutinaria.

Los vehículos y excipientes farmacéuticamente aceptables incluyen todos los aditivos anteriores y similares.

Ejemplos de formulaciones farmacéuticas

A. COMPRIMIDOS	
Componente	**Cantidad por comprimido (mg)**
sustancia activa	100
lactosa	140
almidón de maíz	240
polivinilpirrolidona	15
estearato de magnesio	5
TOTAL	500

Se mezclan la sustancia activa finamente molida, lactosa y parte del almidón de maíz. Se tamiza la mezcla, luego se humedece con una solución de polivinilpirrolidona en agua, se amasa, se granula húmeda y se seca. Los gránulos, el almidón de maíz restante y el estearato de magnesio se tamizan y se mezclan entre sí. Se comprime la mezcla produciendo comprimidos de forma y tamaño adecuado.

B. COMPRIMIDOS	
Componente	**Cantidad por comprimido (mg)**
sustancia activa	80
lactosa	55
almidón de maíz	190
polivinilpirrolidona	15
estearato de magnesio	2
celulosa microcristalina	35
carboximetil almidón sódico	23
TOTAL	400

Se mezclan la sustancia activa finamente molida, parte del almidón de maíz, lactosa, celulosa microcristalina y polivinilpirrolidona, se tamiza la mezcla y se procesa con el resto del almidón de maíz y agua formando un granulado que se seca y tamiza. El carboximetil almidón sódico y el estearato de magnesio se añaden y se combinan y la mezcla se comprime formando comprimidos de tamaño adecuado.

C. COMPRIMIDOS RECUBIERTOS	
Componente	**Cantidad por comprimido (mg)**
sustancia activa	5
lactosa	30
almidón de maíz	41,5
polivinilpirrolidona	3
estearato de magnesio	0,5
TOTAL	90

Se mezclan meticulosamente la sustancia activa, el almidón de maíz, la lactosa y la polivinilpirrolidona y se humedecen con agua. La masa húmeda se hace pasar a través de un tamiz de tamaño de malla 1 mm, se seca a aproximadamente 45ºC y se hacen pasar a continuación los gránulos a través del mismo tamiz. Después de haber mezclado el estearato de magnesio, se comprimen núcleos de comprimidos convexos con un diámetro de 6 mm en una máquina de preparación de comprimidos. Los núcleos de los comprimidos así producidos se revisten de forma conocida con un revestimiento formado esencialmente de azúcar y talco. Los comprimidos revestidos finales se barnizan con cera.

D. CÁPSULAS	
Componente	**Cantidad por cápsula (mg)**
sustancia activa	50
almidón de maíz	268,5
estearato de magnesio	1,5
TOTAL	320

Se mezclan la sustancia y el almidón de maíz y se humedecen con agua. La masa húmeda se tamiza y seca. Los gránulos secos se tamizan y mezclan con estearato de magnesio. La mezcla final se envasa en cápsulas de gelatina dura tamaño 1.

E. SOLUCIÓN PARA AMPOLLA	
Componente	**Cantidad por ampolla**
sustancia activa	50 mg
cloruro sódico	50 mg
agua para inyección	5 ml

498

Se disuelve la sustancia activa en agua a su propio pH u opcionalmente a pH 5,5 a 6,5 y se añade cloruro sódico para hacerla isotónica. La solución obtenida se filtra para que quede exenta de pirógenos y se transfiere el filtrado en condiciones asépticas a ampollas que se esterilizan seguidamente y se cierran por fusión. Las ampollas contienen 5 mg, 25 mg y 50 mg de sustancia activa.

F. SUPOSITORIOS	
Componente	**Cantidad por supositorio (mg)**
sustancia activa	50
grasa sólida	1650
TOTAL	1700

Se funde la grasa sólida. A 40°C, la sustancia activa molida se dispersa de forma homogénea en la misma. La mezcla se enfría hasta 38°C y se vierte en moldes de supositorios ligeramente enfriados.

G. AEROSOL PARA DOSIFICACION	
Componente	**Cantidad**
sustancia activa	0,005
trioleato de sorbitán	0,1
monofluortriclorometano y difluordiclorometano (2:3)	hasta 100

Se transfiere la suspensión a un recipiente convencional de aerosol con una válvula de dosificación. Con preferencia, se liberan por aplicación 50 µl de suspensión. La sustancia activa también se puede dosificar en mayores dosis si se desea (por ejemplo, 0,02% en peso).

H. POLVO PARA INHALACION	
Componente	**Cantidad**
sustancia activa	1,0 mg
lactosa monohidratada	hasta 25 mg

I. POLVO PARA INHALACIÓN	
Componente	**Cantidad**
sustancia activa	2,0 mg
lactosa monohidratada	hasta 25 mg

J. POLVO PARA INHALACIÓN	
Componente	**Cantidad**
sustancia activa	1,0 mg
lactosa monohidratada	hasta 5 mg

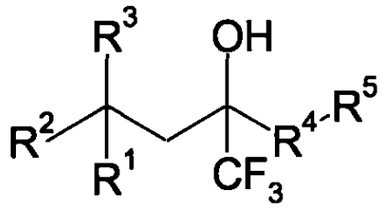
K. POLVO PARA INHALACIÓN	
Componente	**Cantidad**
sustancia activa	2,0 mg
lactosa monohidratada	hasta 5 mg

En los Ejemplos H, I, J y K, el polvo para inhalación se produce de la forma habitual mezclando los ingredientes individuales.

500

REIVINDICACIONES

1. Un compuesto de Fórmula (IA)



(IA)

en la que:

R^1 es un grupo arilo o heteroarilo, cada uno opcionalmente sustituido con uno a tres grupos sustituyentes,

siendo cada grupo sustituyente de R^1 independientemente alquilo C_1-C_5, alquenilo C_2-C_5, alquinilo C_2-C_5, cicloalquilo C_3-C_8, heterociclilo, arilo, heteroarilo, alcoxi C_1-C_5, alqueniloxi C_2-C_5, alquiniloxi C_2-C_5, ariloxi, acilo, alcoxicarbonilo C_1-C_5, alcanoiloxi C_1-C_5, alcanoilo C_1-C_5, aroilo, aminocarbonilo, alquilaminocarbonilo, dialquilaminocarbonilo, aminocarboniloxi, (alquil C_1-C_5)aminocarboniloxi, di(alquil C_1-C_5)aminocarboniloxi, (alcanoil C_1-C_5)amino, (alcoxi C_1-C_5)carbonilamino, (alquil C_1-C_5)sulfonilamino, aminosulfonilo, (alquil C_1-C_5)aminosulfonilo, di(alquil C_1-C_5)aminosulfonilo, halógeno, hidroxi, carboxi, ciano, trifluorometilo, trifluorometoxi, nitro o amino, estando el átomo de nitrógeno opcionalmente mono- o disustituido independientemente con alquilo C_1-C_5 o arilo; o ureido, estando cualquier átomo de nitrógeno opcionalmente sustituido independientemente con alquilo C_1-C_5; o (alquil C_1-C_5)tio, en el que el átomo de azufre está opcionalmente oxidado a un sulfóxido o sulfona,

estando cada grupo sustituyente de R^1 opcionalmente sustituido independientemente con uno a tres grupos sustituyentes seleccionados de metilo, metoxi, halógeno, hidroxi, oxo, ciano o amino,

R^2 y R^3 son cada uno independientemente hidrógeno o alquilo C_1-C_5, o R^2 y R^3 junto con el átomo de carbono al que están unidos en común forman un anillo espiro cicloalquilo C_3-C_8;

R^4 es alquilo C_1-C_5, alquenilo C_2-C_5 o alquinilo C_2-C_5, cada uno opcionalmente sustituido independientemente con uno a tres grupos sustituyentes,

506
591

siendo cada grupo sustituyente de R^4 independientemente alquilo C_1-C_3, hidroxi, halógeno, amino u oxo; y

R^5 es un grupo heteroarilo opcionalmente sustituido independientemente con uno a tres grupos sustituyentes,

siendo cada grupo sustituyente de R^5 independientemente alquilo C_1-C_5, alquenilo C_2-C_5, alquinilo C_2-C_5, cicloalquilo C_3-C_8, heterociclilo, arilo, heteroarilo, alcoxi C_1-C_5, alqueniloxi C_2-C_5, alquiniloxi C_2-C_5, ariloxi, acilo, (alcoxi C_1-C_5)carbonilo, alcanoiloxi C_1-C_5, aminocarbonilo, alquilaminocarbonilo, dialquilaminocarbonilo, aminocarboniloxi, (alquil C_1-C_5)aminocarboniloxi, di(alquil C_1-C_5)aminocarboniloxi, (alcanoil C_1-C_5)amino, (alcoxi C_1-C_5)carbonilamino, (alquil C_1-C_5)sulfonilamino, aminosulfonilo, (alquil C_1-C_5)aminosulfonilo, di(alquil C_1-C_5)aminosulfonilo, halógeno, hidroxi, carboxi, ciano, trifluorometilo, trifluorometoxi, trifluorometiltio, nitro o amino, estando el átomo de nitrógeno opcionalmente mono- o disustituido independientemente con alquilo C_1-C_5; o ureido en el que el átomo de nitrógeno está opcionalmente sustituido independientemente con alquilo C_1-C_5; o (alquil C_1-C_5)tio, en el que el átomo de azufre está opcionalmente oxidado a un sulfóxido o sulfona,

estando cada grupo sustituyente de R^5 opcionalmente sustituido independientemente con uno a tres grupos sustituyentes seleccionados de alquilo C_1-C_3, alcoxi C_1-C_3, halógeno, hidroxi, oxo, ciano, amino o trifluorometilo,

o uno de sus tautómeros, profármacos, solvatos o sales.

2. Un compuesto de Fórmula (IA) según la reivindicación 1, en el que:

R^1 es tienilo, fenilo, naftilo, dihidrobenzofuranilo, benzofuranilo, cromanilo, dihidroindolilo, indolilo, dihidrobenzotienilo, benzotienilo, benzodioxolanilo, dihidrobenzoxazolilo, benzoxazolilo, bencisoxazolilo, benzopirazolilo, bencimidazolilo, quinolinilo, piridinilo, pirimidinilo o pirazinilo, cada uno opcionalmente sustituido independientemente con uno a tres grupos sustituyentes,

siendo cada grupo sustituyente de R^1 independientemente alquilo C_1-C_3,

alquenilo C_2-C_3, alquinilo C_2-C_3, alcoxi C_1-C_3, alqueniloxi C_2-C_3, alcanoilo C_1-C_3, alcoxicarbonilo C_1-C_3 , alcanoiloxi C_1-C_3., halógeno, hidroxi, carboxi, ciano, trifluorometilo, trifluorometoxi, nitro o (alquil C_1-C_3)tio, en el que el átomo de azufre está opcionalmente oxidado a un a sulfóxido o sulfona,

estando cada grupo sustituyente de R^1 opcionalmente sustituido independientemente con un grupo sustituyente seleccionado de metilo, metoxi, halógeno, hidroxi, oxo, ciano o amino;

R^2 y R^3 son cada uno independientemente hidrógeno o alquilo C_1-C_3, o R^2 y R^3 junto con el átomo de carbono al que están unidos en común forman un anillo espiro cicloalquilo C_3-C_6;

R^4 es CH_2; y

R^5 es un grupo imidazolilo, piridilo, indolilo, azaindolilo, diazaindolilo, benzofuranilo, furanopiridinilo, furanopirimidinilo, benzotienilo, tienopiridinilo, tienopirimidinilo, benzoxazolilo, oxazolopiridinilo, benzotiazolilo, tiazolopiridinilo, bencimidazolilo, imidazolopiridinilo, quinolinilo o isoquinolinilo, cada uno opcionalmente sustituido independientemente con uno a tres grupos sustituyentes,

siendo cada grupo sustituyente de R^5 independientemente alquilo C_1-C_3, alquenilo C_2-C_3, fenilo, alcoxi C_1-C_3, metoxicarbonilo, aminocarbonilo, (alquil C_1-C_3)aminocarbonilo, di(alquil C_1-C_3)aminocarbonilo, heterociclilcarbonilo, fluoro, cloro, bromo, oxo, ciano, trifluorometilo o alquil C_1-C_3tio, en el que el átomo de azufre está opcionalmente oxidado a un sulfóxido o sulfona,

estando cada grupo sustituyente de R^5 opcionalmente sustituido independientemente con un grupo sustituyente seleccionado de metilo, metoxi, fluoro, cloro, bromo, oxo o trifluorometilo,

o uno de sus tautómeros, profármacos, solvatos o sales.

3. Un compuesto de Fórmula (IA) según la reivindicación 1, en el que:

R^1 es fenilo, naftilo, piridilo, cromanilo, dihidrobenzofuranilo o benzofuranilo, cada uno

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opcionalmente sustituido independientemente con uno o dos grupos sustituyentes,

siendo cada grupo sustituyente de R^1 independientemente metilo, etilo, metoxi, etoxi, fluoro, cloro, bromo, hidroxi, trifluorometilo, trifluorometoxi o ciano;

R^2 y R^3 son cada uno independientemente metilo, o R^2 y R^3 junto con el átomo de carbono al que están unidos en común forman un anillo espirociclopropilo;

R^4 es CH_2; y

R^5 es un grupo piridilo, indolilo, azaindolilo, benzofuranilo, furanopiridinilo, tienopiridinilo, benzoxazolilo, bencimidazolilo, quinolinilo o isoquinolinilo, cada uno opcionalmente sustituido independientemente con uno a tres grupos sustituyentes,

siendo cada grupo sustituyente de R^5 independientemente metilo, fenilo, metoxicarbonilo, aminocarbonilo, metilaminocarbonilo, dimetilaminocarbonilo, morfolinilcarbonilo, fluoro, cloro, bromo, ciano o trifluorometilo,

o uno de sus tautómeros, profármacos, solvatos o sales.

4. El compuesto de Fórmula (IA) según la reivindicación 1, en el que R^2 y R^3 junto con el átomo de carbono al que están comúnmente unidos forman un anillo espiro cicloalquilo C_3-C_8.

5. El compuesto de Fórmula (IA) según la reivindicación 1, en el que R^2 y R^3 son cada uno independientemente hidrógeno o alquilo C_1-C_5.

6. El compuesto de Fórmula (IA) según la reivindicación 1, en el que R^4 es CH_2.

7. El compuesto de Fórmula (IA) según la reivindicación 1, en el que:

R^1 es fenilo, dihidrobenzofuranilo o benzofuranilo, cada uno independientemente sustituido opcionalmente con uno a tres grupos sustituyentes,

siendo cada grupo sustituyente de R^1 independientemente alquilo C_1-C_3, alquenilo C_2-C_3, alquinilo C_2-C_3, alcoxi C_1-C_3, alqueniloxi C_2-C_3, alcanoilo C_1-

C_3, (alcoxi C_1-C_3)carbonilo, alcanoiloxi C_1-C_3, halógeno, hidroxi, carboxi, ciano, trifluorometilo, nitro o (alquil C_1-C_3)tio, en el que el átomo de azufre está opcionalmente oxidado a un sulfóxido o sulfona; y

R^2 y R^3 son cada uno independientemente hidrógeno o alquilo C_1-C_3,

o uno de sus tautómeros, profármacos, solvatos o sales.

8. Un compuesto seleccionado de:

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-(4,6-dimetilpiridin-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-(piridin-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(6-metilpiridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(4-metilpiridin-2-ilmetil)pentan-2-ol;

4-Fluoro-2-(4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-piridin-2-ilmetilbutil)fenol;

2-(4,5-Dimetiltiazol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

2-(4,5-Dimetiloxazol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(3-metilpiridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(5-metilpiridin-2-ilmetil)pentan-2-ol;

2-Benzotiazol-2-ilmetil-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

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1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(5-fenilbenzoxazol-2-ilmetil)pentan-2-ol;

2-Benzofuran-2-ilmetil-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(3-metilbenzofuran-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-tiofen-2-ilmetilpentan-2-ol;

5-(5-Fluoro-2-metoxifenil)-5-metil-2-piridin-2-il-3-trifluorometilhexan-3-ol;

5-(5-Fluoro-2-metoxifenil)-5-metil-2-piridin-2-il-3-trifluorometilhexan-3-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(5-metilbenzooxazol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(5-metilbenzotiazol-2-ilmetil)pentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(5-metilbenzooxazol-2-ilmetil)butil]fenol;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(5-metilbenzotiazol-2-ilmetil)butil]fenol;

1,1,1-Trifluoro-4-metil-4-fenil-2-piridin-2-ilmetilpentan-2-ol;

2-(4,6-Dimetilpiridin-2-ilmetil)-1,1,1-trifluoro-4-metil-4-fenilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-pirimidin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(4-metilquinolin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1-fenil-1*H*-pirazol-3-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1-metil-1*H*-imidazol-2-ilmetil)pentan-2-ol;

Metilamida del ácido 5-[4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-3-fenilisoxazol-4-carboxílico;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-pirazin-2-ilmetilpentan-2-ol;

4-(2-Aliloxi-5-fluorofenil)-1,1,1-trifluoro-4-metil-2-piridin-2-ilmetilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(3-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

2-Benzooxazol-2-ilmetil-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-piridazin-3-ilmetilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-piridin-3-ilmetilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(5-metilpiridin-3-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-quinolin-2-ilmetilpentan-2-ol;

4-(4-Clorofenil)-1,1,1-trifluoro-4-metil-2-piridin-2-ilmetilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-(6-fluoropiridin-2-ilmetil)-4-metilpentan-2-ol;

6-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]nicotinonitrilo;

2-(1*H*-Indol-2-ilmetil)-1,1,1-trifluoro-4-(4-fluorofenil)-4-metilpentan-2-ol;

2-(6-Cloro-4-trifluorometilpiridin-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

2-(5-Cloro-7-fluoro-1*H*-indol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

4-(3,4-Diclorofenil)-1,1,1-trifluoro-2-(1H-indol-2-ilmetil)-4-metilpentan-2-ol;

2-(2,6-Dicloropiridin-4-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-isoquinolin-1-ilmetil-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

2-[3-(2,6-Dicloropiridin-4-ilmetil)-4,4,4-trifluoro-3-hidroxi-1,1-dimetilbutil]-4-fluorofenol;

4-Fluoro-2-(4,4,4-trifluoro-3-hidroxi-3-isoquinolin-1-ilmetil-1,1-dimetilbutil)fenol;

4-(5-Bromo-2,3-dihidrobenzofuran-7-il)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-piridin-2-ilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(6-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

2-(1*H*-Bencimidazol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(6-fluoro-1*H*-indol-2-ilmetil)-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorofenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

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1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(quinolin-4-ilmetil)pentan-2-ol;

4-(2,3-dihidro-5-cianobenzofuran-7-il)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(2-cloropiridin-4-ilmetil)pentan-2-ol;

4-(3,4-Difluorofenil)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-hidroxifenil)-4-metil-2-(2-cloropiridin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(2-cloropiridin-5-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(2-cloroquinolin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1-oxipiridin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-hidroxifenil)-4-metil-2-(2-cloroquinolin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-(4-metoxifenil)-4-metilpentan-2-ol;

4-[4,4,4-Trifluoro-3-hidroxi-3-(1*H*-indol-2-ilmetil)-1,1-dimetilbutil]fenol;

1,1,1-Trifluoro-2-(5-fluoro-1*H*-indol-2-ilmetil)-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(5-metil-1*H*-indol-2-ilmetil)-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

4-(2,3-dihidrobenzofuran-7-il)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

2-Bencimidazol-1-ilmetil-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1-oxipiridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-metilfenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(6-clorobencimidazol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(2-fluoropiridin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(2-bromopiridin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(7-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(4-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-metil-4-quinolin-4-il-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(5-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(7-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(7-metil-1*H*-benzoimidazol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(6-trifluorometil-1*H*-indol-2-

ilmetil)pentan-2-ol;

1,1,1-Trifluoro-2-quinolin-4-ilmetil-3-[1-(2-trifluorometoxifenil)ciclopropil]propan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(6-trifluorometil-1*H*-benzoimidazol-2-ilmetil)pentan-2-ol;

2-(5-Cloro-6-fluoro-1*H*-benzoimidazol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-3-[1-(5-fluoro-2-metoxifenil)ciclopropil]-2-(1*H*-indol-2-ilmetil)propan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(4-metil-1*H*-indol-2-ilmetil)butil]fenol;

4-Fluoro-2-[4,4,4-trifluoro-3-(7-fluoro-1*H*-indol-2-ilmetil)-3-hidroxi-1,1-dimetilbutil]fenol;

1,1,1-Trifluoro-2-(6-fluoro-1*H*-benzoimidazol-2-ilmetil)-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

2-(6,7-Difluoro-1*H*-benzoimidazol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(5-Bromo-2,3-dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(3-Etil-2-metoxifenil)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

3-[1-(2,5-Difluorofenil)ciclopropil]-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)propan-2-ol;

1,1,1-Trifluoro-3-[1-(4-fluorofenil)ciclopropil]-2-(1*H*-indol-2-ilmetil)propan-2-ol;

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2-Etil-6-(4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-(6-fluoro-4-metil-1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

2-(4,6-Dimetil-1*H*-indol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

4-(3-Etil-2-metoxifenil)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

2-Etil-6-[4,4,4-trifluoro-3-hidroxi-3-(1*H*-indol-2-ilmetil)-1,1-dimetilbutil]fenol;

2-[3-(6,7-Difluoro-1*H*-benzoimidazol-2-ilmetil)-4,4,4-trifluoro-3-hidroxi-1,1-dimetilbutil]-4-fluorofenol;

2-(7-Cloro-5-trifluorometil-1*H*-benzoimidazol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

2-(5,7-Dimetil-1*H*-benzoimidazol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-(5-fluoro-2-metilfenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-(4-fluorofenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-(3-fluorofenil)-4-metilpentan-2-ol;

2-[3-(5,7-Dimetil-1*H*-benzoimidazol-2-ilmetil)-4,4,4-trifluoro-3-hidroxi-1,1-dimetilbutil]-4-fluorofenol;

1,1,1-Trifluoro-4-(3-metoxifenil)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-(3-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-4-metil-2-(4-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorofenil)-4-metil-2-(4-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorofenil)-4-metil-2-(4-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-metil-2-quinolin-4-ilmetil-4-(3-trifluorometilfenil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-4-metil-2-(5-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorofenil)-4-metil-2-(5-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorofenil)-4-metil-2-(5-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-4-metil-2-(7-metil-1*H*-benzoimidazol-2-ilmetil)pentan-2-ol;

2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-3*H*-benzoimidazol-5-carbonitrilo;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-(3-trifluorometilfenil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

5-Fluoro-2-(4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(5-trifluorometil-1*H*-indol-2-ilmetil)butil]fenol;

4-(5-Bromo-4-fluoro-2-metoxifenil)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-

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2-ol;

2-(6-Cloro-4-metil-1*H*-indol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

2-(2-Fenil-4-metilimidazol-1-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihidrobenzofuran-7-il)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

2-(2-Fenilimidazol-1-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihidrobenzofuran-7-il)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-metil-4-(5-metil-2,3-dihidrobenzofuran-7-il)-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-fenilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-(5-metil-2,3-dihidrobenzofuran-7-il)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-(7-fluoro-4-metil-1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-*m*-tolilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-naftalen-2-ilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-*o*-tolilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-*p*-tolilpentan-2-ol;

4-(2,3-Dihidrobenzofuran-5-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(7-Bromo-2,3-dihidrobenzofuran-5-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(2,3-Dihidrobenzofuran-5-il)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(1-metoxinaftalen-2-il)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

2-(4,4,4-Trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)naftalen-1-ol;

1,1,1-Trifluoro-4-metil-4-naftalen-2-il-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-7-carbonitrilo;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-(1-metoxinaftalen-2-il)-4-metilpentan-2-ol;

2-[4,4,4-Trifluoro-3-hidroxi-3-(1*H*-indol-2-ilmetil)-1,1-dimetilbutil]naftalen-1-ol;

1,1,1-Trifluoro-4-metil-2-quinolin-4-ilmetil-4-*p*-tolilpentan-2-ol;

4-Croman-8-il-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-4-metil-4-fenil-2-quinolin-4-ilmetilpentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)butil]fenol;

4-(6-Bromocroman-8-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)butil]fenol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[3,2-*b*]piridin-2-ilmetil)pentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[3,2-*b*]piridin-2-ilmetil)butil]fenol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[2,3-*b*]piridin-2-ilmetil)pentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[2,3-*b*]piridin-2-ilmetil)butil]fenol;

1,1,1-Trifluoro-4-(3-fluorofenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorofenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-metil-4-fenil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-(7-fluoroquinolin-4-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorofenil)-2-(7-fluoroquinolin-4-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorofenil)-2-(5-fluoroquinolin-4-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-4-metilquinolin-8-il)-4-(4-fluorofenil)-4-metilpentan-2-ol;

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2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

2-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

2-[4-(5-Fluoro-2-metilfenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

1,1,1-Trifluoro-4-(2-metoxifenil)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-(2-metoxifenil)-4-metilpentan-2-ol;

2-[4-(5-Fluoro-2,3-dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

4-(5-Bromo-2-metoxifenil)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(5-Bromo-2-metoxifenil)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

2-(4,4,4-Trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

1,1,1-Trifluoro-4-metil-4-fenil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

2-[4-(5-Bromo-2,3-dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

4-Bromo-2-(4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

2-[4-(4-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

2-(2-Hidroxi-4-metil-4-fenil-2-trifluorometilpentil)-4-metil-1*H*-indol-6-carbonitrilo;

2-[4-(3-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

2-[4-(4-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

2-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-metil-4-fenil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorofenil)-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

2-(2-Hidroxi-4-metil-4-fenil-2-trifluorometilpentil)-1*H*-indol-5-carbonitrilo;

2-[4-(3-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

2-[4-(4-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-(5,6,7,8-tetrahidroquinolin-4-ilmetil)pentan-2-ol;

1-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

2-(2-Hidroxi-4-metil-4-fenil-2-trifluorometilpentil)-1*H*-indol-3-carbonitrilo;

5-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[2,3-*c*]piridin-2-

ilmetil)butil]fenol;

2-[4-(4-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

2-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

2-[4-(3-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

2-[4-(4-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

2-[4-(5-Fluoro-2-metilfenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-(4-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-metil-4-fenilpentan-2-ol;

Éster metílico del ácido 2-[4-(4-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carboxílico;

1-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(3-metil-1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-(5-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol;

4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-(5-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(3-metoxifenil)-4-metil-2-(5-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol;

5-Fluoro-2-[4,4,4-trifluoro-3-(7-fluoro-1*H*-indol-2-ilmetil)-3-hidroxi-1,1-dimetilbutil]fenol;

2-[2-Hidroxi-4-(3-metoxifenil)-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

2-[4-(5-Fluoro-2-hidroxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(3-metil-1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)butil]fenol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-tiofen-3-ilpentan-2-ol;

1,1,1-Trifluoro-4-metil-2-quinolin-4-ilmetil-4-tiofen-3-ilpentan-2-ol;

5-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)butil]fenol;

1,1,1-Trifluoro-4-(3-fluorofenil)-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

2-[4-(4-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

3-(4,4,4-Trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(4-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol;

4-(5-Bromo-2-metoxifenil)-1,1,1-trifluoro-4-metil-2-(5-trifluorometil-1*H*-indol-2-

ilmetil)pentan-2-ol;

2-[4-(5-Bromo-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

Éster metílico del ácido 2-[4-(5-bromo-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carboxílico;

Éster metílico del ácido 2-[4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carboxílico;

4-(2,6-Dimetilfenil)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

3-[4,4,4-Trifluoro-3-hidroxi-3-(1*H*-indol-2-ilmetil)-1,1-dimetilbutil]fenol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihidrobenzofuran-7-il)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

Éster metílico del ácido 1-[4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carboxílico;

2-[2-Hidroxi-4-(3-metoxifenil)-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

2-[4-(5-Bromo-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

2-[4-(4-Fluoro-2-hidroxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(5-nitro-1*H*-indol-2-ilmetil)pentan-2-ol;

Amida del ácido 2-[4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carboxílico;

Dimetilamida del ácido 2-[4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-

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trifluorometilpentil]-1*H*-indol-5-carboxílico;

{2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-il}*morfolin-4-ilmetanona*;

Éster metílico del ácido 2-[4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-6-carboxílico;

Éster metílico del ácido 2-[4-(5-fluoro-2-hidroxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-6-carboxílico;

Ácido 2-[4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-6-carboxílico; y

Ácido 2-[4-(5-fluoro-2-hidroxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-6-carboxílico,

o uno de sus tautómeros, profármacos, solvatos o sales.

9. Un compuesto seleccionado de:

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-(piridin-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(5-fenilbenzoxazol-2-ilmetil)pentan-2-ol;

2-Benzofuran-2-ilmetil-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(3-metilbenzofuran-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(3-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1-metil-1*H*-indol-2-

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ilmetil)pentan-2-ol;

6-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]nicotinonitrilo;

2-(1*H*-Indol-2-ilmetil)-1,1,1-trifluoro-4-(4-fluorofenil)-4-metilpentan-2-ol;

2-(6-Cloro-4-trifluorometilpiridin-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

2-(5-Cloro-7-fluoro-1*H*-indol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

4-(3,4-Diclorofenil)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

2-(2,6-Dicloropiridin-4-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

2-[3-(2,6-Dicloropiridin-4-ilmetil)-4,4,4-trifluoro-3-hidroxi-1,1-dimetilbutil]-4-fluorofenol;

4-Fluoro-2-(4,4,4-trifluoro-3-hidroxi-3-isoquinolin-1-ilmetil-1,1-dimetilbutil)fenol;

4-(5-Bromo-2,3-dihidrobenzofuran-7-il)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-piridin-2-ilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(6-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

2-(1*H*-Bencimidazol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(6-fluoro-1*H*-indol-2-ilmetil)-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

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1,1,1-Trifluoro-4-(3-fluorofenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(quinolin-4-ilmetil)pentan-2-ol;

4-(2,3-dihidro-5-cianobenzofuran-7-il)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(2-cloropiridin-4-ilmetil)pentan-2-ol;

4-(3,4-Difluorofenil)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-hidroxifenil)-4-metil-2-(2-cloropiridin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(2-cloroquinolin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-hidroxifenil)-4-metil-2-(2-cloroquinolin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-(4-metoxifenil)-4-metilpentan-2-ol;

4-[4,4,4-Trifluoro-3-hidroxi-3-(1*H*-indol-2-ilmetil)-1,1-dimetilbutil]fenol;

1,1,1-Trifluoro-2-(5-fluoro-1*H*-indol-2-ilmetil)-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(5-metil-1*H*-indol-2-ilmetil)-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

4-(2,3-dihidrobenzofuran-7-il)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

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2-Bencimidazol-1-ilmetil-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-metilfenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(6-clorobencimidazol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(2-fluoropiridin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(2-bromopiridin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(7-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(4-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(5-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(7-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(7-metil-1*H*-benzoimidazol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(6-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(6-trifluorometil-1*H*-benzoimidazol-2-ilmetil)pentan-2-ol;

2-(5-Cloro-6-fluoro-1*H*-benzoimidazol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-3-[1-(5-fluoro-2-metoxifenil)ciclopropil]-2-(1*H*-indol-2-ilmetil)propan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(4-metil-1*H*-indol-2-ilmetil)butil]fenol;

4-Fluoro-2-[4,4,4-trifluoro-3-(7-fluoro-1*H*-indol-2-ilmetil)-3-hidroxi-1,1-dimetilbutil]fenol;

1,1,1-Trifluoro-2-(6-fluoro-1*H*-benzoimidazol-2-ilmetil)-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

2-(6,7-Difluoro-1*H*-benzoimidazol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(5-Bromo-2,3-dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(3-Etil-2-metoxifenil)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-3-[1-(4-fluorofenil)ciclopropil]-2-(1*H*-indol-2-ilmetil)propan-2-ol;

2-Etil-6-(4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-(6-fluoro-4-metil-1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

2-(4,6-Dimetil-1*H*-indol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

4-(3-Etil-2-metoxifenil)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

2-Etil-6-[4,4,4-trifluoro-3-hidroxi-3-(1*H*-indol-2-ilmetil)-1,1-dimetilbutil]fenol;

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2-[3-(6,7-Difluoro-1*H*-benzoimidazol-2-ilmetil)-4,4,4-trifluoro-3-hidroxi-1,1-dimetilbutil]-4-fluorofenol;

2-(7-Cloro-5-trifluorometil-1*H*-benzoimidazol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

2-(5,7-Dimetil-1*H*-benzoimidazol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-(5-fluoro-2-metilfenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-(4-fluorofenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-(3-fluorofenil)-4-metilpentan-2-ol;

2-[3-(5,7-Dimetil-1*H*-benzoimidazol-2-ilmetil)-4,4,4-trifluoro-3-hidroxi-1,1-dimetilbutil]-4-fluorofenol;

1,1,1-Trifluoro-4-(3-metoxifenil)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-(3-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-4-metil-2-(4-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorofenil)-4-metil-2-(4-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorofenil)-4-metil-2-(4-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-metil-2-quinolin-4-ilmetil-4-(3-trifluorometilfenil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-4-metil-2-(5-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorofenil)-4-metil-2-(5-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorofenil)-4-metil-2-(5-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-4-metil-2-(7-metil-1*H*-benzoimidazol-2-ilmetil)pentan-2-ol;

2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-3*H*-benzoimidazol-5-carbonitrilo;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-(3-trifluorometilfenil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

5-Fluoro-2-(4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(5-trifluorometil-1*H*-indol-2-ilmetil)butil]fenol;

4-(5-Bromo-4-fluoro-2-metoxifenil)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

2-(6-Cloro-4-metil-1*H*-indol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

2-(2-Fenil-4-metilimidazol-1-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihidrobenzofuran-7-il)-4-metil-2-quinolin-4-

ilmetilpentan-2-ol;

2-(2-Fenilimidazol-1-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihidrobenzofuran-7-il)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-metil-4-(5-metil-2,3-dihidrobenzofuran-7-il)-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-fenilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-(5-metil-2,3-dihidrobenzofuran-7-il)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-(7-fluoro-4-metil-1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-*m*-tolilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-naftalen-2-ilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-*o*-tolilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-*p*-tolilpentan-2-ol;

4-(2,3-Dihidrobenzofuran-5-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(7-Bromo-2,3-dihidrobenzofuran-5-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(2,3-Dihidrobenzofuran-5-il)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(1-metoxinaftalen-2-il)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

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2-(4,4,4-Trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)naftalen-1-ol;

1,1,1-Trifluoro-4-metil-4-naftalen-2-il-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-7-carbonitrilo;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-(1-metoxinaftalen-2-il)-4-metilpentan-2-ol;

2-[4,4,4-Trifluoro-3-hidroxi-3-(1*H*-indol-2-ilmetil)-1,1-dimetilbutil]naftalen-1-ol;

1,1,1-Trifluoro-4-metil-2-quinolin-4-ilmetil-4-*p*-tolilpentan-2-ol;

4-Croman-8-il-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-4-metil-4-fenil-2-quinolin-4-ilmetilpentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)butil]fenol;

4-(6-Bromocroman-8-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)butil]fenol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[3,2-*b*]piridin-2-ilmetil)pentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[3,2-*b*]piridin-2-ilmetil)butil]fenol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[2,3-*b*]piridin-2-ilmetil)pentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[2,3-*b*]piridin-2-ilmetil)butil]fenol;

1,1,1-Trifluoro-4-(3-fluorofenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorofenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-metil-4-fenil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-(7-fluoroquinolin-4-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorofenil)-2-(7-fluoroquinolin-4-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorofenil)-2-(5-fluoroquinolin-4-ilmetil)-4-metilpentan-2-ol;

2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

2-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

2-[4-(5-Fluoro-2-metilfenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

1,1,1-Trifluoro-4-(2-metoxifenil)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-(2-metoxifenil)-4-metilpentan-2-ol;

2-[4-(5-Fluoro-2,3-dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

4-(5-Bromo-2-metoxifenil)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(5-Bromo-2-metoxifenil)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

2-(4,4,4-Trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

1,1,1-Trifluoro-4-metil-4-fenil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

2-[4-(5-Bromo-2,3-dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

4-Bromo-2-(4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

2-[4-(4-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometil-pentil]-1*H*-indol-3-carbonitrilo;

2-(2-Hidroxi-4-metil-4-fenil-2-trifluorometilpentil)-4-metil-1*H*-indol-6-carbonitrilo;

2-[4-(3-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

2-[4-(4-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

2-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-metil-4-fenil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorofenil)-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

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4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

2-(2-Hidroxi-4-metil-4-fenil-2-trifluorometilpentil)-1*H*-indol-5-carbonitrilo;

2-[4-(3-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

2-[4-(4-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-(5,6,7,8-tetrahidroquinolin-4-ilmetil)pentan-2-ol;

1-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

2-(2-Hidroxi-4-metil-4-fenil-2-trifluorometilpentil)-1*H*-indol-3-carbonitrilo;

5-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)butil]fenol;

2-[4-(4-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

2-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

2-[4-(3-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

2-[4-(4-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

2-[4-(5-Fluoro-2-metilfenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

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4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-(4-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-metil-4-fenilpentan-2-ol;

Éster metílico del ácido 2-[4-(4-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carboxílico;

1-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(3-metil-1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-(5-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol;

4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-(5-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(3-metoxifenil)-4-metil-2-(5-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol;

2-[2-Hidroxi-4-(3-metoxifenil)-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

5-Fluoro-2-[4,4,4-trifluoro-3-(7-fluoro-1*H*-indol-2-ilmetil)-3-hidroxi-1,1-dimetilbutil]fenol;

2-[4-(5-Fluoro-2-hidroxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

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4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(3-metil-1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)butil]fenol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-tiofen-3-ilpentan-2-ol;

1,1,1-Trifluoro-4-metil-2-quinolin-4-ilmetil-4-tiofen-3-ilpentan-2-ol;

5-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)butil]fenol;

1,1,1-Trifluoro-4-(3-fluorofenil)-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

2-[4-(4-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

3-(4,4,4-Trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(4-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol;

4-(5-Bromo-2-metoxifenil)-1,1,1-trifluoro-4-metil-2-(5-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol;

2-[4-(5-Bromo-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

Éster metílico del ácido 2-[4-(5-bromo-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carboxílico;

Éster metílico del ácido 2-[4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carboxílico;

4-(2,6-Dimetilfenil)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

3-[4,4,4-Trifluoro-3-hidroxi-3-(1*H*-indol-2-ilmetil)-1,1-dimetilbutil]fenol;

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1,1,1-Trifluoro-4-(5-fluoro-2,3-dihidrobenzofuran-7-il)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol; y

Éster metílico del ácido 1-[4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carboxílico,

o uno de sus tautómeros, profármacos, solvatos o sales.

10. Un compuesto seleccionado de:

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

2-(2,6-Dicloropiridin-4-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

2-[3-(2,6-Dicloropiridin-4-ilmetil)-4,4,4-trifluoro-3-hidroxi-1,1-dimetilbutil]-4-fluorofenol;

4-(5-Bromo-2,3-dihidrobenzofuran-7-il)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

2-(1*H*-Bencimidazol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorofenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(quinolin-4-ilmetil)pentan-2-ol;

4-(2,3-dihidro-5-cianobenzofuran-7-il)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(2-cloropiridin-4-ilmetil)pentan-2-ol;

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1,1,1-Trifluoro-4-(5-fluoro-2-hidroxifenil)-4-metil-2-(2-cloropiridin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(2-cloroquinolin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-hidroxifenil)-4-metil-2-(2-cloroquinolin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-(4-metoxifenil)-4-metilpentan-2-ol;

4-[4,4,4-Trifluoro-3-hidroxi-3-(1*H*-indol-2-ilmetil)-1,1-dimetilbutil]fenol;

1,1,1-Trifluoro-2-(5-fluoro-1*H*-indol-2-ilmetil)-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

4-(2,3-dihidrobenzofuran-7-il)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(2-bromopiridin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(7-metil-1*H*-benzoimidazol-2-ilmetil)pentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(4-metil-1*H*-indol-2-ilmetil)butil]fenol;

4-Fluoro-2-[4,4,4-trifluoro-3-(7-fluoro-1*H*-indol-2-ilmetil)-3-hidroxi-1,1-dimetilbutil]fenol;

1,1,1-Trifluoro-2-(6-fluoro-1*H*-benzoimidazol-2-ilmetil)-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

2-(6,7-Difluoro-1*H*-benzoimidazol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(5-Bromo-2,3-dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(3-Etil-2-metoxifenil)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

2-Etil-6-(4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

2-Etil-6-[4,4,4-trifluoro-3-hidroxi-3-(1*H*-indol-2-ilmetil)-1,1-dimetilbutil]fenol;

2-(5,7-Dimetil-1*H*-benzoimidazol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

2-[3-(5,7-Dimetil-1*H*-benzoimidazol-2-ilmetil)-4,4,4-trifluoro-3-hidroxi-1,1-dimetilbutil]-4-fluorofenol;

1,1,1-Trifluoro-4-(3-metoxifenil)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-(3-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-4-metil-2-(4-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorofenil)-4-metil-2-(4-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorofenil)-4-metil-2-(4-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-metil-2-quinolin-4-ilmetil-4-(3-trifluorometilfenil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-4-metil-2-(7-metil-1*H*-benzoimidazol-2-

ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-(3-trifluorometilfenil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

5-Fluoro-2-(4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

4-(5-Bromo-4-fluoro-2-metoxifenil)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

2-(2-Fenil-4-metilimidazol-1-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihidrobenzofuran-7-il)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

2-(2-Fenilimidazol-1-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihidrobenzofuran-7-il)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-metil-4-(5-metil-2,3-dihidrobenzofuran-7-il)-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-fenilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-(5-metil-2,3-dihidrobenzofuran-7-il)pentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-*m*-tolilpentan-2-ol;

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1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-naftalen-2-ilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-*o*-tolilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-*p*-tolilpentan-2-ol;

4-(2,3-Dihidrobenzofuran-5-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(7-Bromo-2,3-dihidrobenzofuran-5-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(2,3-Dihidrobenzofuran-5-il)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(1-metoxinaftalen-2-il)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

2-(4,4,4-Trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)naftalen-1-ol;

1,1,1-Trifluoro-4-metil-4-naftalen-2-il-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-(1-metoxinaftalen-2-il)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-metil-2-quinolin-4-ilmetil-4-*p*-tolilpentan-2-ol;

4-Croman-8-il-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-4-metil-4-fenil-2-quinolin-4-ilmetilpentan-2-ol;

4-(6-Bromocroman-8-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[3,2-*b*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[2,3-*b*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorofenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-metil-4-fenil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-(7-fluoroquinolin-4-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorofenil)-2-(7-fluoroquinolin-4-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorofenil)-2-(5-fluoroquinolin-4-ilmetil)-4-metilpentan-2-ol;

2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

2-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

2-[4-(5-Fluoro-2-metilfenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

1,1,1-Trifluoro-4-(2-metoxifenil)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-(2-metoxifenil)-4-metilpentan-2-ol;

2-[4-(5-Fluoro-2,3-dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

4-(5-Bromo-2-metoxifenil)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(5-Bromo-2-metoxifenil)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

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2-(4,4,4-Trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

1,1,1-Trifluoro-4-metil-4-fenil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

2-[4-(5-Bromo-2,3-dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

4-Bromo-2-(4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

1,1,1-Trifluoro-4-(4-fluorofenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

2-[4-(4-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometil-pentil]-1*H*-indol-3-carbonitrilo;

2-(2-Hidroxi-4-metil-4-fenil-2-trifluorometilpentil)-4-metil-1*H*-indol-6-carbonitrilo;

2-[4-(3-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

2-[4-(4-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

2-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-metil-4-fenil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

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2-(2-Hidroxi-4-metil-4-fenil-2-trifluorometilpentil)-1*H*-indol-5-carbonitrilo;

2-[4-(3-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

2-[4-(4-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-(5,6,7,8-tetrahidroquinolin-4-ilmetil)pentan-2-ol;

1-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

2-(2-Hidroxi-4-metil-4-fenil-2-trifluorometilpentil)-1*H*-indol-3-carbonitrilo;

5-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)butil]fenol;

2-[4-(4-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

2-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

2-[4-(3-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

2-[4-(4-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

2-[4-(5-Fluoro-2-metilfenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

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4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)butil]fenol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-metil-4-fenilpentan-2-ol;

Éster metílico del ácido 2-[4-(4-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carboxílico;

1-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(3-metil-1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(3-metoxifenil)-4-metil-2-(5-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol;

2-[2-Hidroxi-4-(3-metoxifenil)-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)butil]fenol;

5-Fluoro-2-[4,4,4-trifluoro-3-(7-fluoro-1*H*-indol-2-ilmetil)-3-hidroxi-1,1-dimetilbutil]fenol;

2-[4-(5-Fluoro-2-hidroxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(3-metil-1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)butil]fenol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-tiofen-3-ilpentan-2-ol;

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1,1,1-Trifluoro-4-metil-2-quinolin-4-ilmetil-4-tiofen-3-ilpentan-2-ol;

5-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)butil]fenol;

1,1,1-Trifluoro-4-(3-fluorofenil)-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

3-(4,4,4-Trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

Éster metílico del ácido 2-[4-(5-bromo-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carboxílico;

Éster metílico del ácido 2-[4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carboxílico;

4-(2,6-Dimetilfenil)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

3-[4,4,4-Trifluoro-3-hidroxi-3-(1*H*-indol-2-ilmetil)-1,1-dimetilbutil]fenol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihidrobenzofuran-7-il)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

2-[2-Hidroxi-4-(3-metoxifenil)-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

2-[4-(5-Bromo-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

2-[4-(4-Fluoro-2-hidroxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(5-nitro-1*H*-indol-2-ilmetil)pentan-2-ol;

Amida del ácido 2-[4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carboxílico;

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Dimetilamida del ácido 2-[4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carboxílico;

{2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-il}morfolin-4-ilmetanona;

Éster metílico del ácido 2-[4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-6-carboxílico;

Éster metílico del ácido 2-[4-(5-fluoro-2-hidroxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-6-carboxílico;

Ácido 2-[4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-6-carboxílico; y

Ácido 2-[4-(5-fluoro-2-hidroxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-6-carboxílico,

o uno de sus tautómeros, profármacos, solvatos o sales.

11. Un compuesto seleccionado de:

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

2-(2,6-Dicloropiridin-4-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

2-[3-(2,6-Dicloropiridin-4-ilmetil)-4,4,4-trifluoro-3-hidroxi-1,1-dimetilbutil]-4-fluorofenol;

4-(5-Bromo-2,3-dihidrobenzofuran-7-il)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

2-(1*H*-Bencimidazol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-

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metilpentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorofenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(quinolin-4-ilmetil)pentan-2-ol;

4-(2,3-dihidro-5-cianobenzofuran-7-il)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(2-cloropiridin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-hidroxifenil)-4-metil-2-(2-cloropiridin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(2-cloroquinolin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-hidroxifenil)-4-metil-2-(2-cloroquinolin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-(4-metoxifenil)-4-metilpentan-2-ol;

4-[4,4,4-Trifluoro-3-hidroxi-3-(1*H*-indol-2-ilmetil)-1,1-dimetilbutil]fenol;

1,1,1-Trifluoro-2-(5-fluoro-1*H*-indol-2-ilmetil)-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

4-(2,3-dihidrobenzofuran-7-il)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(2-bromopiridin-4-ilmetil)pentan-2-ol;

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1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(7-metil-1*H*-benzoimidazol-2-ilmetil)pentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(4-metil-1*H*-indol-2-ilmetil)butil]fenol;

4-Fluoro-2-[4,4,4-trifluoro-3-(7-fluoro-1*H*-indol-2-ilmetil)-3-hidroxi-1,1-dimetilbutil]fenol;

1,1,1-Trifluoro-2-(6-fluoro-1*H*-benzoimidazol-2-ilmetil)-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

2-(6,7-Difluoro-1*H*-benzoimidazol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(5-Bromo-2,3-dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(3-Etil-2-metoxifenil)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

2-Etil-6-(4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

2-Etil-6-[4,4,4-trifluoro-3-hidroxi-3-(1*H*-indol-2-ilmetil)-1,1-dimetilbutil]fenol;

2-(5,7-Dimetil-1*H*-benzoimidazol-2-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

2-[3-(5,7-Dimetil-1*H*-benzoimidazol-2-ilmetil)-4,4,4-trifluoro-3-hidroxi-1,1-dimetilbutil]-4-fluorofenol;

1,1,1-Trifluoro-4-(3-metoxifenil)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-(3-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-

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ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-4-metil-2-(4-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorofenil)-4-metil-2-(4-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorofenil)-4-metil-2-(4-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-metil-2-quinolin-4-ilmetil-4-(3-trifluorometilfenil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-4-metil-2-(7-metil-1*H*-benzoimidazol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-(3-trifluorometilfenil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

5-Fluoro-2-(4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

4-(5-Bromo-4-fluoro-2-metoxifenil)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

2-(2-Fenil-4-metilimidazol-1-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihidrobenzofuran-7-il)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

2-(2-Fenilimidazol-1-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

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1,1,1-Trifluoro-4-(5-fluoro-2,3-dihidrobenzofuran-7-il)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-metil-4-(5-metil-2,3-dihidrobenzofuran-7-il)-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-fenilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-(5-metil-2,3-dihidrobenzofuran-7-il)pentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-*m*-tolilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-naftalen-2-ilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-*o*-tolilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-*p*-tolilpentan-2-ol;

4-(2,3-Dihidrobenzofuran-5-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(7-Bromo-2,3-dihidrobenzofuran-5-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(2,3-Dihidrobenzofuran-5-il)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(1-metoxinaftalen-2-il)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

2-(4,4,4-Trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)naftalen-1-ol;

1,1,1-Trifluoro-4-metil-4-naftalen-2-il-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-

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carbonitrilo;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-(1-metoxinaftalen-2-il)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-metil-2-quinolin-4-ilmetil-4-*p*-tolilpentan-2-ol;

4-Croman-8-il-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-4-metil-4-fenil-2-quinolin-4-ilmetilpentan-2-ol;

4-(6-Bromocroman-8-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[3,2-*b*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[2,3-*b*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorofenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-metil-4-fenil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-(7-fluoroquinolin-4-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorofenil)-2-(7-fluoroquinolin-4-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorofenil)-2-(5-fluoroquinolin-4-ilmetil)-4-metilpentan-2-ol;

2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

2-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

2-[4-(5-Fluoro-2-metilfenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-

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6-carbonitrilo;

1,1,1-Trifluoro-4-(2-metoxifenil)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-(2-metoxifenil)-4-metilpentan-2-ol;

2-[4-(5-Fluoro-2,3-dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

4-(5-Bromo-2-metoxifenil)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(5-Bromo-2-metoxifenil)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

2-(4,4,4-Trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

1,1,1-Trifluoro-4-metil-4-fenil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

2-[4-(5-Bromo-2,3-dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

4-Bromo-2-(4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

1,1,1-Trifluoro-4-(4-fluorofenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

2-[4-(4-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometil-pentil]-1*H*-indol-3-carbonitrilo;

2-(2-Hidroxi-4-metil-4-fenil-2-trifluorometilpentil)-4-metil-1*H*-indol-6-carbonitrilo;

2-[4-(3-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

2-[4-(4-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-

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carbonitrilo;

2-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-metil-4-fenil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

2-(2-Hidroxi-4-metil-4-fenil-2-trifluorometilpentil)-1*H*-indol-5-carbonitrilo;

2-[4-(3-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1 *H*-indol-3-carbonitrilo;

2-[4-(4-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-(5,6,7,8-tetrahidroquinolin-4-ilmetil)pentan-2-ol;

1-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

2-(2-Hidroxi-4-metil-4-fenil-2-trifluorometilpentil)-1*H*-indol-3-carbonitrilo;

5-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)butil]fenol;

2-[4-(4-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

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2-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

2-[4-(3-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

2-[4-(4-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

2-[4-(5-Fluoro-2-metilfenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)butil]fenol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-metil-4-fenilpentan-2-ol;

Éster metílico del ácido 2-[4-(4-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carboxílico;

1-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(3-metil-1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(3-metoxifenil)-4-metil-2-(5-trifluorometil-1*H*-indol-2-ilmetil)pentan-2-ol;

2-[2-Hidroxi-4-(3-metoxifenil)-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)butil]fenol;

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5-Fluoro-2-[4,4,4-trifluoro-3-(7-fluoro-1*H*-indol-2-ilmetil)-3-hidroxi-1,1-dimetilbutil]fenol;

2-[4-(5-Fluoro-2-hidroxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(3-metil-1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)butil]fenol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-tiofen-3-ilpentan-2-ol;

1,1,1-Trifluoro-4-metil-2-quinolin-4-ilmetil-4-tiofen-3-ilpentan-2-ol;

5-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)butil]fenol;

1,1,1-Trifluoro-4-(3-fluorofenil)-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

3-(4,4,4-Trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

Éster metílico del ácido 2-[4-(5-bromo-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carboxílico;

Éster metílico del ácido 2-[4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carboxílico;

4-(2,6-Dimetilfenil)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

3-[4,4,4-Trifluoro-3-hidroxi-3-(1*H*-indol-2-ilmetil)-1,1-dimetilbutil]fenol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihidrobenzofuran-7-il)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

2-[2-Hidroxi-4-(3-metoxifenil)-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

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2-[4-(5-Bromo-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

2-[4-(4-Fluoro-2-hidroxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(5-nitro-1*H*-indol-2-ilmetil)pentan-2-ol;

Amida del ácido 2-[4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carboxílico;

Dimetilamida del ácido 2-[4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carboxílico;

{2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-il}morfolin-4-ilmetanona;

Éster metílico del ácido 2-[4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-6-carboxílico; y

Éster metílico del ácido 2-[4-(5-fluoro-2-hidroxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-6-carboxílico,

o uno de sus tautómeros, profármacos, solvatos o sales.

12. Un compuesto seleccionado de:

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

2-(2,6-Dicloropiridin-4-ilmetil)-1,1,1-trifluoro-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

4-(5-Bromo-2,3-dihidrobenzofuran-7-il)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-

metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(quinolin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-2-(7-fluoro-1*H*-indol-2-ilmetil)-4-(5-fluoro-2-metoxifenil)-4-metilpentan-2-ol;

4-(2,3-dihidrobenzofuran-7-il)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(4-metil-1*H*-indol-2-ilmetil)butil]fenol;

4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(5-Bromo-2,3-dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

2-[3-(5,7-Dimetil-1*H*-benzoimidazol-2-ilmetil)-4,4,4-trifluoro-3-hidroxi-1,1-dimetilbutil]-4-fluorofenol;

1,1,1-Trifluoro-4-(3-metoxifenil)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-(3-metoxifenil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-4-metil-2-(4-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorofenil)-4-metil-2-(4-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(3-fluorofenil)-4-metil-2-(4-metil-1*H*-indol-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-metil-2-quinolin-4-ilmetil-4-(3-trifluorometilfenil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-(3-trifluorometilfenil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

5-Fluoro-2-(4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

4-(5-Bromo-4-fluoro-2-metoxifenil)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihidrobenzofuran-7-il)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2,3-dihidrobenzofuran-7-il)-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-metil-4-(5-metil-2,3-dihidrobenzofuran-7-il)-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-(5-metil-2,3-dihidrobenzofuran-7-il)pentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-*m*-tolilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-metil-4-*o*-tolilpentan-2-ol;

4-(7-Bromo-2,3-dihidrobenzofuran-5-il)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-

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carbonitrilo;

1,1,1-Trifluoro-4-metil-4-fenil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-2-(7-fluoroquinolin-4-ilmetil)-4-metilpentan-2-ol;

1,1,1-Trifluoro-4-(4-fluorofenil)-2-(5-fluoroquinolin-4-ilmetil)-4-metilpentan-2-ol;

2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

2-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

2-[4-(5-Fluoro-2-metilfenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

1,1,1-Trifluoro-4-(2-metoxifenil)-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

1,1,1-Trifluoro-2-(1*H*-indol-2-ilmetil)-4-(2-metoxifenil)-4-metilpentan-2-ol;

2-[4-(5-Fluoro-2,3-dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

4-(5-Bromo-2-metoxifenil)-1,1,1-trifluoro-4-metil-2-quinolin-4-ilmetilpentan-2-ol;

4-(5-Bromo-2-metoxifenil)-1,1,1-trifluoro-2-(1*H*-indol-2-ilmetil)-4-metilpentan-2-ol;

2-(4,4,4-Trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

1,1,1-Trifluoro-4-metil-4-fenil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

2-[4-(5-Bromo-2,3-dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

4-Bromo-2-(4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-quinolin-4-ilmetilbutil)fenol;

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4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

2-[4-(4-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometil-pentil]-1*H*-indol-3-carbonitrilo;

2-(2-Hidroxi-4-metil-4-fenil-2-trifluorometilpentil)-4-metil-1*H*-indol-6-carbonitrilo;

2-[4-(3-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

2-[4-(4-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

2-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-metil-4-fenil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

4-(2,3-Dihidrobenzofuran-7-il)-1,1,1-trifluoro-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

2-(2-Hidroxi-4-metil-4-fenil-2-trifluorometilpentil)-1*H*-indol-5-carbonitrilo;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-(5,6,7,8-tetrahidroquinolin-4-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(4-fluoro-2-metoxifenil)-4-metil-2-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)pentan-2-ol;

5-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)butil]fenol;

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2-[4-(4-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

2-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

2-[4-(4-Fluorofenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

2-[4-(5-Fluoro-2-metilfenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[3,2-*c*]piridin-2-ilmetil)butil]fenol;

1-[4-(2,3-Dihidrobenzofuran-7-il)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-3-carbonitrilo;

1,1,1-Trifluoro-4-(5-fluoro-2-metilfenil)-4-metil-2-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(3-metil-1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)pentan-2-ol;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)butil]fenol;

2-[4-(5-Fluoro-2-hidroxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

4-Fluoro-2-[4,4,4-trifluoro-3-hidroxi-1,1-dimetil-3-(1*H*-pirrolo[2,3-*c*]piridin-2-ilmetil)butil]fenol;

2-[2-Hidroxi-4-(3-metoxifenil)-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

2-[4-(5-Bromo-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-4-metil-1*H*-indol-6-carbonitrilo;

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2-[4-(4-Fluoro-2-hidroxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carbonitrilo;

1,1,1-Trifluoro-4-(5-fluoro-2-metoxifenil)-4-metil-2-(5-nitro-1*H*-indol-2-ilmetil)pentan-2-ol;

Amida del ácido 2-[4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carboxílico;

Dimetilamida del ácido 2-[4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-carboxílico;

{2-[4-(5-Fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-5-il}morfolin-4-ilmetanona;

Éster metílico del ácido 2-[4-(5-fluoro-2-metoxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-6-carboxílico;

Éster metílico del ácido 2-[4-(5-fluoro-2-hidroxifenil)-2-hidroxi-4-metil-2-trifluorometilpentil]-1*H*-indol-6-carboxílico,

o uno de sus tautómeros, profármacos, solvatos o sales.

13. Una composición farmacéutica que comprende una cantidad eficaz de un compuesto según una de las reivindicaciones 1 a 12, o uno de sus tautómeros, profármacos, solvatos o sales, y un excipiente o vehículo farmacéuticamente aceptable.

14. Un procedimiento para modular la función del receptor de glucocorticoides en un paciente, comprendiendo el procedimiento administrar al paciente una cantidad eficaz de un compuesto farmacéuticamente aceptable según una de las reivindicaciones 1 a 12, o uno de sus tautómeros, profármacos, solvatos o sales.

15. Un procedimiento para tratar un estado de enfermedad o trastorno mediado por la función del receptor de glucocorticoides en un paciente que necesita dicho tratamiento, comprendiendo el procedimiento administrar al paciente una cantidad eficaz de un compuesto farmacéuticamente aceptable según una de las reivindicaciones

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1 a 12, o uno de sus tautómeros, profármacos, solvatos o sales.

16. Un procedimiento para tratar un estado de enfermedad o trastorno seleccionado de: diabetes tipo II, obesidad, enfermedades cardiovasculares, hipertensión, arteriosclerosis, enfermedades neurológicas, tumores suprarrenales y pituitarios y glaucoma en un paciente que necesita dicho tratamiento, comprendiendo el procedimiento administrar al paciente una cantidad eficaz de un compuesto farmacéuticamente aceptable según una de las reivindicaciones 1 a 12, o uno de sus tautómeros, profármacos, solvatos o sales.

17. Un procedimiento para tratar una enfermedad caracterizada por procesos inflamatorios, alérgicos o proliferativos en un paciente que necesita dicho tratamiento, comprendiendo el procedimiento administrar al paciente una cantidad eficaz de un compuesto farmacéuticamente aceptable según una de las reivindicaciones 1 a 12, o uno de sus tautómeros, profármacos, solvatos o sales.

18. Procedimiento según la reivindicación 17, en el que la enfermedad se selecciona de: (i) enfermedades del pulmón; (ii) enfermedades reumáticas/enfermedades autoinmunes/enfermedades de las articulaciones; (iii) enfermedades alérgicas; (iv) enfermedades por vasculitis; (v) enfermedades dermatológicas; (vi) enfermedades renales; (vii) enfermedades hepáticas; (viii) enfermedades gastrointestinales; (ix) enfermedades proctológicas; (x) enfermedades oculares; (xi) enfermedades del área del oído, nariz y garganta (ORL); (xii) enfermedades neurológicas; (xiii) enfermedades de la sangre; (xiv) enfermedades tumorales; (xv) enfermedades endocrinas; (xvi) enfermedades de trasplantes de órganos y tejidos y de injerto contra huésped; (xvii) estados severos de shock; (xviii) terapia de sustitución; y (xix) dolor de génesis inflamatoria.

19. Procedimiento según la reivindicación 17, en el que la enfermedad se selecciona de: diabetes tipo I, osteoartritis, síndrome de Guillain-Barre, restenosis después de una angioplastia coronaria percutánea transluminal, enfermedad de Alzheimer, dolor agudo y crónico, aterosclerosis, lesión por reperfusión, enfermedades de resorción ósea, insuficiencia cardíaca congestiva, infarto de miocardio, lesión por calor, lesión en varios órganos secundaria a un traumatismo, meningitis purulenta aguda, enterocolitis necrotizante y síndromes asociados con hemodiálisis, leucoféresis y transfusión de granulocitos.

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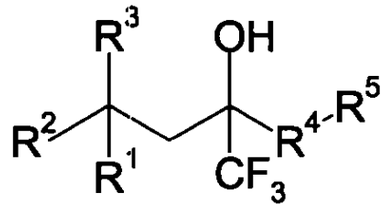
20. Un procedimiento para tratar un estado de enfermedad o trastorno mediado por la función del receptor de glucocorticoides en un paciente que necesita dicho tratamiento, comprendiendo el procedimiento administrar de forma secuencial o simultánea al paciente (a) una cantidad eficaz de un compuesto farmacéuticamente aceptable según una de las reivindicaciones 1 a 12 o uno de sus tautómeros, profármacos, solvatos o sales; y (b) un glucocorticoide farmacéuticamente aceptable.

21. Un kit para la determinación diagnóstica *in vitro* de la función del receptor de glucocorticoides en una muestra, que comprende:

(a) una cantidad eficaz para el diagnóstico de un compuesto según la reivindicación 1 o uno de sus tautómeros, profármacos, solvatos o sales; y

(b) instrucciones para usar el kit de diagnóstico.

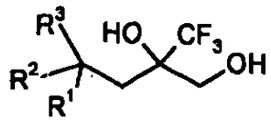
22. Un procedimiento para preparar un compuesto de Fórmula (IA)



(IA)

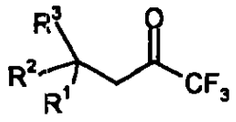
en la que R^1, R^2, R^3, R^4 y R^5 son como se han definido antes, comprendiendo el procedimiento:

(a) hacer reaccionar un éster de Fórmula (II) con un agente reductor adecuado en un disolvente adecuado, formando un diol de Fórmula (III)



III

(b) hacer reaccionar el diol de Fórmula (III) en condiciones adecuadas de ruptura oxidativa, formando una cetona de Fórmula (IV)

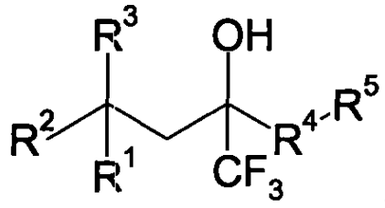


IV ; y

(c) hacer reaccionar la cetona de Fórmula (IV) con un compuesto organometálico adecuado R^5R^4M en el que M es Li o MgX y X es Cl, Br o I, en un disolvente

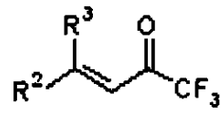
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adecuado, formando el compuesto de Fórmula (IA)



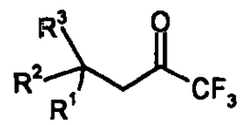
; o

(a') hacer reaccionar la trifluoroacetamida de Fórmula (X) con un bromuro de vinil-magnesio que tenga R^2 y R^3 en un disolvente adecuado, proporcionando la trifluorometilenona de Fórmula (XI)



XI ;

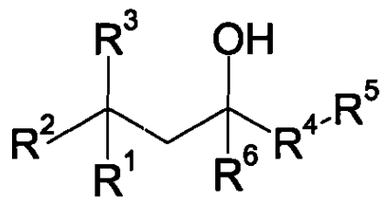
(b') hacer reaccionar la trifluorometilenona de Fórmula (XI) con un reactivo de organocobre generado a partir de un reactivo organometálico R^5R^4M en el que M es Li o MgX y una sal de cobre CuX, en la que X es Cl, Br o I, en un disolvente adecuado, formando una cetona de Fórmula (IV)



IV ;

y llevar a cabo la etapa (c) como se ha descrito antes.

23. Un compuesto de Fórmula (IB)



(IB)

en la que:

R^1 es un grupo arilo o heteroarilo, cada uno opcionalmente sustituido independientemente con uno a tres grupos sustituyentes,

siendo cada grupo sustituyente de R^1 independientemente alquilo C_1-C_5, alquenilo C_2-C_5, alquinilo C_2-C_5, cicloalquilo C_3-C_8, heterociclilo, arilo,

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heteroarilo, alcoxi C_1-C_5, alqueniloxi C_2-C_5, alquiniloxi C_2-C_5 , ariloxi, acilo, (alcoxi C_1-C_5)carbonilo, alcanoiloxi C_1-C_5, alcanoilo C_1-C_5, aroilo, aminocarbonilo, (alquil C_1-C_5)aminocarbonilo, di(alquil C_1-C_5)aminocarbonilo, aminocarboniloxi, (alquil C_1-C_5)aminocarboniloxi, di(alquil C_1-C_5)aminocarboniloxi, (alcanoil C_1-C_5)amino, (alcoxi C_1-C_5)carbonilamino, (alquil C_1-C_5)sulfonilamino, aminosulfonilo, (alquil C_1-C_5)aminosulfonilo, di(alquil C_1-C_5)aminosulfonilo, halógeno, hidroxi, carboxi, ciano, trifluorometilo, trifluorometoxi, nitro o amino, estando el átomo de nitrógeno opcionalmente mono- o disustituido independientemente con alquilo C_1-C_5 o arilo; o ureido, en el que el átomo de nitrógeno está opcionalmente sustituido independientemente con alquilo C_1-C_5; o (alquil C_1-C_5)tio, en el que el átomo de azufre está opcionalmente oxidado a un sulfóxido o sulfona,

estando cada grupo sustituyente de R^1 opcionalmente sustituido independientemente con uno a tres grupos sustituyentes seleccionados de metilo, metoxi, halógeno, hidroxi, oxo, ciano o amino,

R^2 y R^3 son cada uno independientemente alquilo C_1-C_5;

R^4 es alquilo C_1-C_5, alquenilo C_2-C_5 o alquinilo C_2-C_5, cada uno opcionalmente sustituido independientemente con uno a tres grupos sustituyentes,

siendo cada grupo sustituyente de R^4 independientemente alquilo C_1-C_3, hidroxi, halógeno, amino u oxo;

R^5 es un grupo heteroarilo sustituido opcionalmente independientemente con uno a tres grupos sustituyentes,

siendo cada grupo sustituyente de R^5 independientemente alquilo C_1-C_5, alquenilo C_2-C_5, alquinilo C_2-C_5, cicloalquilo C_3-C_8, heterociclilo, arilo, heteroarilo, alcoxi C_1-C_5, alqueniloxi C_2-C_5, alquiniloxi C_2-C_5, ariloxi, acilo, (alcoxi C_1-C_5)carbonilo, alcanoiloxi C_1-C_5, aminocarbonilo, alquilaminocarbonilo, dialquilaminocarbonilo, aminocarboniloxi, (alquil C_1-

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C_5)aminocarboniloxi, di(alquil C_1-C_5)aminocarboniloxi, (alcanoil C_1-C_5)amino, (alcoxi C_1-C_5)carbonilamino, (alquil C_1-C_5)sulfonilamino, (alquil C_1-C_5)aminosulfonilo, di(alquil C_1-C_5)aminosulfonilo, halógeno, hidroxi, carboxi, ciano, trifluorometilo, trifluorometoxi, trifluorometiltio, nitro o amino, estando el átomo de nitrógeno opcionalmente mono- o disustituido independientemente con alquilo C_1-C_5; o ureido en el que el átomo de nitrógeno está opcionalmente sustituido independientemente con alquilo C_1-C_5; o alquil C_1-C_5, en el que el átomo de azufre está opcionalmente oxidado a un sulfóxido o sulfona,

estando cada grupo sustituyente de R^5 opcionalmente sustituido independientemente con uno a tres grupos sustituyentes seleccionados de alquilo C_1-C_3, alcoxi C_1-C_3, halógeno, hidroxi, oxo, ciano, amino o trifluorometilo; y

R^6 es alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, carbociclo, heterociclilo, arilo, heteroarilo, carbociclo-alquilo C_1-C_8, aril-alquilo C_1-C_8, aril-haloalquilo C_1-C_8, heterociclil-alquilo C_1-C_8, heteroaril-alquilo C_1-C_8, carbociclo-alquenilo C_2-C_8, aril-alquenilo C_2-C_8, heterociclil-alquenilo C_2-C_8 o heteroaril-alquenilo C_2-C_8, cada uno opcionalmente sustituido independientemente con uno a tres grupos sustituyentes,

siendo cada grupo sustituyente de R^6 es independientemente alquilo C_1-C_5, alquenilo C_2-C_5, alquinilo C_2-C_5, cicloalquilo C_3-C_8, fenilo, alcoxi C_1-C_5, fenoxi, alcanoilo C_1-C_5, aroilo, (alcoxi C_1-C_5)carbonilo, alcanoiloxi C_1-C_5, aminocarboniloxi, (alquil C_1-C_5)aminocarboniloxi, di(alquil C_1-C_5)aminocarboniloxi, aminocarbonilo, (alquil C_1-C_5)aminocarbonilo, di(alquil C_1-C_5)aminocarbonilo, (alcanoil C_1-C_5)amino, (alcoxi C_1-C_5)carbonilamino, (alquil C_1-C_5)sulfonilamino, (alquil C_1-C_5)aminosulfonilo, di(alquil C_1-C_5)aminosulfonilo, halógeno, hidroxi, carboxi, ciano, oxo, trifluorometilo, nitro, amino, estando el átomo de nitrógeno opcionalmente mono- o disustituido independientemente con alquilo C_1-C_5; o ureido en el que el átomo de nitrógeno está opcionalmente sustituido independientemente con alquilo C_1-C_5; o alquiltio C_1-C_5 en el que el átomo de azufre está opcionalmente oxidado a un sulfóxido o sulfona,

no pudiendo ser R^6 trifluorometilo,

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o uno de sus tautómeros, profármacos, solvatos o sales.

24. El compuesto de Fórmula (IB) según la reivindicación 23, en el que:

R^1 es tienilo, fenilo, dihidrobenzofuranilo, benzofuranilo, dihidroindolilo, indolilo, dihidrobenzotienilo, benzotienilo, benzodioxolanilo, benzoxazolilo, bencisoxazolilo, benzopirazolilo, bencimidazolilo, quinolinilo, piridinilo, pirimidinilo o pirazinilo, cada uno opcionalmente sustituido independientemente con uno a tres grupos sustituyentes,

siendo cada grupo sustituyente de R^1 independientemente alquilo C_1-C_3, alquenilo C_2-C_3, alquinilo C_2-C_3, alcoxi C_1-C_3, alqueniloxi C_2-C_3, alcanoilo C_1-C_3, (alcoxi C_1-C_3)carbonilo, alcanoiloxi C_1-C_3, halógeno, hidroxi, carboxi, ciano, trifluorometilo, nitro o (alquil C_1-C_3)tio, en el que el átomo de azufre está opcionalmente oxidado a un sulfóxido o sulfona,

estando cada grupo sustituyente de R^1 opcionalmente sustituido independientemente con un grupo sustituyente seleccionado de metilo, metoxi, halógeno, hidroxi, oxo, ciano o amino;

R^2 y R^3 son cada uno independientemente alquilo C_1-C_3;

R^4 es CH_2;

R^5 es un grupo piridilo, indolilo, azaindolilo, benzofuranilo, furanilpiridinilo, benzotienilo, tienopiridinilo, benzoxazolilo, benzotiazolilo, bencimidazolilo, quinolinilo o isoquinolinilo, cada uno opcionalmente sustituido independientemente con uno a tres grupos sustituyentes,

siendo cada grupo sustituyente de R^5 independientemente alquilo C_1-C_3, alquenilo C_2-C_3, fenilo, alcoxi C_1-C_3, metoxicarbonilo, aminocarbonilo, (alquil C_1-C_3)aminocarbonilo, di(alquil C_1-C_3)aminocarbonilo, heterociclilcarbonilo, fluoro, cloro, bromo, ciano, trifluorometilo o (alquil C_1-C_3)tio, en el que el átomo de azufre está opcionalmente oxidado a un sulfóxido o sulfona,

estando cada grupo sustituyente de R^5 opcionalmente sustituido

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independientemente con un grupo sustituyente seleccionado de metilo, metoxi, fluoro, cloro, bromo o trifluorometilo; y

R^6 es alquilo C_1-C_5, alquenilo C_2-C_5, cicloalquilo C_3-C_6, fenilo, cicloalquil C_3-C_6-alquilo C_1-C_3, fenil-alquilo C_1-C_3, fenil-haloalquilo C_1-C_3, cicloalquil C_3-C_6-alquenilo C_2-C_3, fenil-alquenilo C_2-C_3, cada uno opcionalmente sustituido independientemente con uno a tres grupos sustituyentes,

siendo cada grupo sustituyente de R^6 independientemente alquilo C_1-C_3, alquenilo C_2-C_3, alquinilo C_2-C_3, alcoxi C_1-C_3, aminocarbonilo, (alquil C_1-C_3)aminocarbonilo, di(alquil C_1-C_3)aminocarbonilo, halógeno, hidroxi, carboxi, ciano, trifluorometilo, nitro o alquiltio C_1-C_3, en el que el átomo de azufre está opcionalmente oxidado a un sulfóxido o sulfona,

o uno de sus tautómeros, profármacos, solvatos o sales.

25. El compuesto de Fórmula (IB) según la reivindicación 23, en el que:

R^1 es tienilo, fenilo, piridilo, dihidrobenzofuranilo o benzofuranilo, cada uno opcionalmente sustituido independientemente con uno o dos grupos sustituyentes,

siendo cada grupo sustituyente de R^1 independientemente metilo, etilo, metoxi, etoxi, fluoro, cloro, bromo, hidroxi, trifluorometilo o ciano;

R^2 y R^3 son cada uno metilo;

R^4 es CH_2;

R^5 es un grupo piridilo, indolilo, azaindolilo, benzofuranilo, benzoxazolilo, bencimidazolilo, quinolinilo o isoquinolinilo, cada uno opcionalmente sustituido independientemente con uno a tres grupos sustituyentes,

siendo cada grupo sustituyente de R^5 independientemente metilo, fenilo, metoxicarbonilo, aminocarbonilo, metilaminocarbonilo, dimetilaminocarbonilo, morfolinilcarbonilo, fluoro, cloro, ciano o trifluorometilo; y

R^6 es alquilo C_1-C_5, cicloalquilo C_3-C_6, cicloalquil C_3-C_6-metil- o bencilo, cada uno

opcionalmente sustituido independientemente con uno a tres grupos sustituyentes,

siendo cada grupo sustituyente de R^6 independientemente metilo, metoxi, fluoro, cloro, bromo, ciano, trifluorometilo o hidroxi,

o uno de sus tautómeros, profármacos, solvatos o sales.

26. El compuesto de Fórmula (IB) según la reivindicación 23, en el que R^4 es CH_2.

27. El compuesto de Fórmula (IB) según la reivindicación 23, en el que:

R^1 es tienilo, fenilo, dihidrobenzofuranilo o benzofuranilo, cada uno opcionalmente sustituido independientemente con uno a tres grupos sustituyentes,

siendo cada grupo sustituyente de R^1 independientemente alquilo C_1-C_3, alquenilo C_2-C_3, alquinilo C_2-C_3, alcoxi C_1-C_3, alqueniloxi C_2-C_3, alcanoilo C_1-C_3, (alcoxi C_1-C_3)carbonilo, alcanoiloxi C_1-C_3, halógeno, hidroxi, carboxi, ciano, trifluorometilo, nitro o (alquil C_1-C_3)tio en el que el átomo de azufre está opcionalmente oxidado a un sulfóxido o sulfona; y

R^2 y R^3 son cada uno independientemente alquilo C_1-C_3,

o uno de sus tautómeros, profármacos, solvatos o sales.

28. Un compuesto seleccionado de:

2-Ciclopropil-4-(5-fluoro-2-metoxifenil)-1-(1*H*-indol-2-il)-4-metilpentan-2-ol;

5-(5-Fluoro-2-metoxifenil)-3-(1*H*-indol-2-ilmetil)-2,5-dimetilhexan-3-ol;

5-(5-Fluoro-2-metoxifenil)-3-(1*H*-indol-2-ilmetil)-5-metilhexan-3-ol;

2-Ciclohexilmetil-1-(4,6-dimetil-piridin-2-il)-4-(5-fluoro-2-metoxi-fenil)-4-metil-pentan-2-ol;

2-Ciclohexilmetil-4-(5-fluoro-2-metoxi-fenil)-1-(1*H*-indol-2-il)-4-metil-pentan-2-ol;

7-(5-Fluoro-2-metoxifenil)-5-(indol-2-ilmetil)-7-metiloctan-5-ol;

2-(Bencimidazol-2-ilmetil)-4-metil-4-(pirrol-1-il)pentan-2-ol;

1-(1*H*-Benzoimidazol-2-il)-2-ciclohexilmetil-4-(5-fluoro-2-metoxi-fenil)-4-metil-pentan-2-ol;

5-(5-Fluoro-2-metoxifenil)-3-(bencimidazol-2-ilmetil)-2,2,5-trimetilhexan-3-ol;

4-(5-Fluoro-2-metoxifenil)-2-fluorometil-1-(1*H*-indol-2-il)-4-metilpentan-2-ol;

2-Ciclopropil-4-(2,3-dihidrobenzofuran-7-il)-1-(1*H*-indol-2-il)-4-metilpentan-2-ol;

2-Ciclopropil-4-(2,3-dihidrobenzofuran-7-il)-1-(quinolin-4-il)-4-metilpentan-2-ol;

2-Ciclopropil-4-(5-fluoro-2-metoxifenil)-1-(6-ciano-4-metilindol-2-il)-4-metilpentan-2-ol;

2-Ciclopropil-4-(5-fluoro-2-metoxifenil)-4-metil-1-(1*H*-pirrolo[2,3-*c*]piridin-2-il)pentan-2-ol;

4-(5-Bromo-2,3-dihidrobenzofuran-7-il)-2-ciclopropil-4-metil-1-(1*H*-pirrolo[2,3-*c*]piridin-2-il)pentan-2-ol,

o uno de sus tautómeros, profármacos, solvatos o sales.

29. Un compuesto seleccionado de:

2-Ciclopropil-4-(5-fluoro-2-metoxifenil)-1-(1*H*-indol-2-il)-4-metilpentan-2-ol;

5-(5-Fluoro-2-metoxifenil)-3-(indol-2-ilmetil)-2,5-dimetilhexan-3-ol;

5-(5-Fluoro-2-metoxifenil)-3-(indol-2-ilmetil)-5-metilhexan-3-ol;

2-Ciclohexilmetil-4-(5-fluoro-2-metoxifenil)-1-(1*H*-indol-2-il)-4-metilpentan-2-ol;

5-(5-Fluoro-2-metoxifenil)-3-(bencimidazol-2-ilmetil)-2,2,5-trimetilhexan-3-ol;

4-(5-Fluoro-2-metoxifenil)-2-fluorometil-1-(1*H*-indol-2-il)-4-metilpentan-2-ol;

2-Ciclopropil-4-(2,3-dihidrobenzofuran-7-il)-1-(1*H*-indol-2-il)-4-metilpentan-2-ol;

2-Ciclopropil-4-(2,3-dihidrobenzofuran-7-il)-1-(quinolin-4-il)-4-metilpentan-2-ol;

2-Ciclopropil-4-(5-fluoro-2-metoxifenil)-1-(6-ciano-4-metilindol-2-il)-4-metilpentan-2-ol;

2-Ciclopropil-4-(5-fluoro-2-metoxifenil)-4-metil-1-(1*H*-pirrolo[2,3-*c*]piridin-2-il)pentan-2-ol; y

4-(5-Bromo-2,3-dihidrobenzofuran-7-il)-2-ciclopropil-4-metil-1-(1*H*-pirrolo[2,3-*c*]piridin-2-il)pentan-2-ol,

o uno de sus tautómeros, profármacos, solvatos o sales.

30. Un compuesto seleccionado de:

2-Ciclopropil-4-(5-fluoro-2-metoxifenil)-4-metil-1-(1*H*-pirrolo[2,3-*c*]piridin-2-il)pentan-2-ol; y

2-Ciclopropil-4-(2,3-dihidrobenzofuran-7-il)-1-(1*H*-indol-2-il)-4-metilpentan-2-ol,

o uno de sus tautómeros, profármacos, solvatos o sales.

31. Un compuesto seleccionado de:

5-(5-Fluoro-2-metoxifenil)-3-(bencimidazol-2-ilmetil)-2,2,5-trimetilhexan-3-ol;

4-(5-Fluoro-2-metoxifenil)-2-fluorometil-1-(1*H*-indol-2-il)-4-metilpentan-2-ol;

2-Ciclopropil-4-(5-fluoro-2-metoxifenil)-1-(1*H*-indol-2-il)-4-metilpentan-2-ol;

5-(5-Fluoro-2-metoxifenil)-3-(indol-2-ilmetil)-2,5-dimetilhexan-3-ol;

5-(5-Fluoro-2-metoxifenil)-3-(indol-2-ilmetil)-5-metilhexan-3-ol; y

2-Ciclopropil-4-(5-fluoro-2-metoxifenil)-4-metil-1-(1*H*-pirrolo[2,3-*c*]piridin-2-il)pentan-2-ol,

o uno de sus tautómeros, profármacos, solvatos o sales.

32. Un compuesto seleccionado de:

2-Ciclopropil-4-(5-fluoro-2-metoxifenil)-4-metil-1-(1*H*-pirrolo[2,3-*c*]piridin-2-il)pentan-2-ol;

2-Ciclopropil-4-(5-fluoro-2-metoxifenil)-1-(1*H*-indol-2-il)-4-metilpentan-2-ol,

o uno de sus tautómeros, profármacos, solvatos o sales.

33. Una composición farmacéutica que comprende una cantidad eficaz de un compuesto según una de las reivindicaciones 23 a 32, o uno de sus tautómeros, profármacos, solvatos o sales, y un excipiente o vehículo farmacéuticamente aceptable.

34. Un procedimiento para modular la función del receptor de glucocorticoides en un paciente, comprendiendo el procedimiento administrar al paciente una cantidad eficaz de un compuesto farmacéuticamente aceptable según una de las reivindicaciones 23 a 32, o uno de sus tautómeros, profármacos, solvatos o sales.

35. Un procedimiento para tratar un estado de enfermedad o trastorno mediado por la función del receptor de glucocorticoides en un paciente que necesita dicho tratamiento, comprendiendo el procedimiento administrar al paciente una cantidad eficaz de un compuesto farmacéuticamente aceptable según una de las reivindicaciones 23 a 32, o uno de sus tautómeros, profármacos, solvatos o sales.

36. Un procedimiento para tratar un estado de enfermedad o trastorno seleccionado de: diabetes tipo II, obesidad, enfermedades cardiovasculares, hipertensión, arteriosclerosis, enfermedades neurológicas, tumores suprarrenales y pituitarios y glaucoma en un paciente que necesita dicho tratamiento, comprendiendo el procedimiento administrar al paciente una cantidad eficaz de un compuesto farmacéuticamente aceptable según una de las reivindicaciones 23 a 32, o uno de sus

tautómeros, profármacos, solvatos o sales.

37. Un procedimiento para tratar una enfermedad caracterizada por procesos inflamatorios, alérgicos o proliferativos en un paciente que necesita dicho tratamiento, comprendiendo el procedimiento administrar al paciente una cantidad eficaz de un compuesto farmacéuticamente aceptable según una de las reivindicaciones 23 a 32, o uno de sus tautómeros, profármacos, solvatos o sales.

38. Procedimiento según la reivindicación 37, en el que la enfermedad se selecciona de: (i) enfermedades del pulmón; (ii) enfermedades reumáticas/enfermedades autoinmunes/enfermedades de las articulaciones; (iii) enfermedades alérgicas; (iv) enfermedades por vasculitis; (v) enfermedades dermatológicas; (vi) enfermedades renales; (vii) enfermedades hepáticas; (viii) enfermedades gastrointestinales; (ix) enfermedades proctológicas; (x) enfermedades oculares; (xi) enfermedades del área del oído, nariz y garganta (ORL); (xii) enfermedades neurológicas; (xiii) enfermedades de la sangre; (xiv) enfermedades tumorales; (xv) enfermedades endocrinas; (xvi) enfermedades de trasplantes de órganos y tejidos y de injerto contra huésped; (xvii) estados severos de shock; (xviii) terapia de sustitución; y (xix) dolor de génesis inflamatoria.

39. Procedimiento según la reivindicación 37, en el que la enfermedad se selecciona de: diabetes tipo I, osteoartritis, síndrome de Guillain-Barre, restenosis después de una angioplastia coronaria percutánea transluminal, enfermedad de Alzheimer, dolor agudo y crónico, aterosclerosis, lesión por reperfusión, enfermedades de resorción ósea, insuficiencia cardíaca congestiva, infarto de miocardio, lesión por calor, lesión en varios órganos secundaria a un traumatismo, meningitis purulenta aguda, enterocolitis necrotizante y síndromes asociados con hemodiálisis, leucoféresis y transfusión de granulocitos.

40. Un procedimiento para tratar un estado de enfermedad o trastorno mediado por la función del receptor de glucocorticoides en un paciente que necesita dicho tratamiento, comprendiendo el procedimiento administrar de forma secuencial o simultánea al paciente (a) una cantidad eficaz de un compuesto farmacéuticamente aceptable según una de las reivindicaciones 23 a 32 o uno de sus tautómeros, profármacos, solvatos o sales; y (b) un glucocorticoide farmacéuticamente aceptable.

41. Un kit para la determinación diagnóstica *in vitro* de la función del receptor de

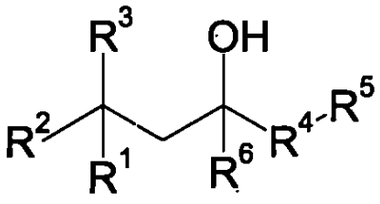
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glucocorticoides en una muestra, que comprende:

(a) una cantidad eficaz para el diagnóstico de un compuesto según la reivindicación 23 o uno de sus tautómeros, profármacos, solvatos o sales; y

(b) instrucciones para usar el kit de diagnóstico.

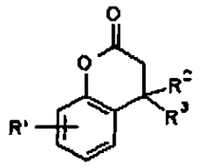
42. Un procedimiento para preparar un compuesto de Fórmula (IB)



(IB)

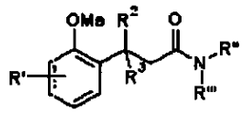
en la que R^1 es un grupo 2-metoxifenilo opcionalmente sustituido y R^2, R^3, R^4, R^5 y R^6 son como se definen en la reivindicación 23, comprendiendo el procedimiento:

(a) hacer reaccionar un fenol opcionalmente sustituido de Fórmula (XXII) con un cloruro de acriloilo de Fórmula (XIII) en presencia de una base adecuada, seguido por ciclación del éster intermedio por tratamiento con un ácido de Lewis adecuado, formando una lactona de Fórmula (XIV)



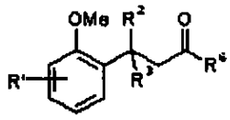
XIV ;

(b) hacer reaccionar la lactona de Fórmula (XIV) con una amina adecuada HNR'R'', seguido por tratamiento del fenol intermedio con yoduro de metilo en presencia de una base adecuada formando una amida de Fórmula (XV)



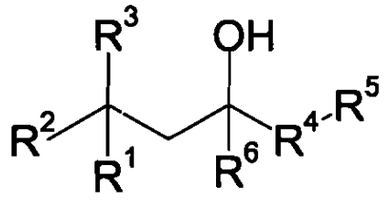
XV ;

(c) hacer reaccionar la amida de Fórmula (XV) con un reactivo organometálico adecuado R^6M, en el que M es Li o MgX y X es Cl, Br o I, en un disolvente adecuado formando una cetona de Fórmula (XVI)

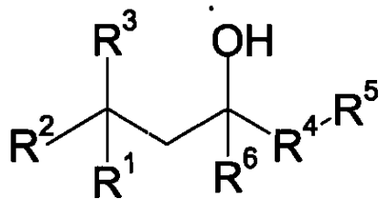


XVI ;

(d) hacer reaccionar la cetona de Fórmula (XVI) con un reactivo organometálico adecuado R^5R^4M en el que M es Li o MgX y X es Cl, Br o I, en un disolvente adecuado formando un compuesto de Fórmula (IB)



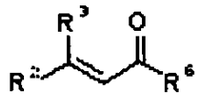
43. Un procedimiento para preparar un compuesto de Fórmula (IB):



(IB)

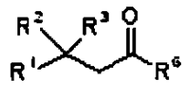
en la que R^1, R^2, R^3, R^4, R^5 y R^6 son como se definen en la reivindicación 23, comprendiendo el procedimiento:

(a') hacer reaccionar una amida de Fórmula (XVII) con un bromuro de vinil magnesio que tiene R^2 y R^3 de Fórmula (XVIII) en un disolvente adecuado, proporcionando una enona de Fórmula (XIX)



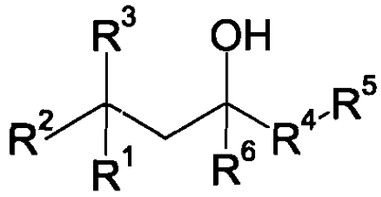
XIX ;

(b') hacer reaccionar la enona de Fórmula (XIX) con un reactivo de organocobre adecuado generado a partir de un reactivo organometálico R^1M, en el que M es Li o MgX, y una sal de cobre CuX, en la que X es Cl, Br o I, en un disolvente adecuado, formando una cetona de Fórmula (XX)



XX ; y

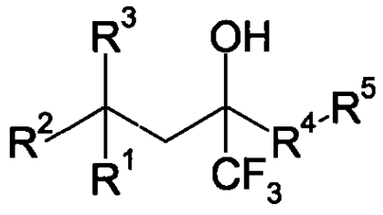
(c') hacer reaccionar la cetona de Fórmula (XX) con un reactivo organometálico adecuado R^5R^4M, en el que M es Li o MgX, y X es Cl, Br o I, en un disolvente adecuado, formando el compuesto de Fórmula (IB)



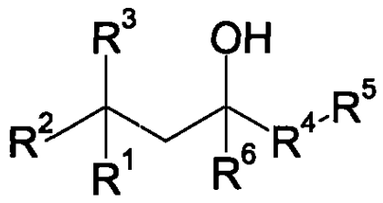
517

Resumen

Compuestos de Fórmula (IA) y Fórmula (IB)



(IA)



(IB)

en las que R^1, R^2, R^3, R^4, R^5 y R^6 son como se definen en la presente memoria para la Fórmula (IA) o la Fórmula (IB), o uno de sus tautómeros, profármacos, solvatos o sales; composiciones farmacéuticas que contienen dichos compuestos y procedimientos para modular la función del receptor de glucocorticoides y procedimientos para tratar estados de enfermedad o trastornos mediados por la función del receptor de glucocorticoides o caracterizados por procesos inflamatorios, alérgicos o proliferativos en un paciente usando estos compuestos.

COLO 07612-841-006-5
PRP/WPCL7612/ID-000218

578

Industria y Comercio
SUPERINTENDENCIA

FORMATO DE DIGITALIZACION
RELACION DE ANEXOS

Royal Technologies S.A.

Item	Expediente No	04106799.	No de Folio
		No de unidades	√
1	CD		
2	DVD		
3	REVISTA		
4	LIBRO		
5	PERIODICO		
6	DISQUETES		
7	SOBRE DE MANILA		
8	SOBRE BLANCO TAMAÑO CARTA	1	
9	SOBRE BLANCO TAMAÑO OFICIO		
10	OTROS:		

Observaciones:

Arte final.

579
N

NIT : 800176089-2

SUPERINDUSTRIA Y COMERCIO

Folios: 579

RECIBO OFICIAL DE CAJA : 04 - 77,850
FECHA : OCTUBRE 4 DE 2004

Radicacion : 04105799 00000000
Fecha (AMD): 2004-10-21 16:54:58
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	32758685	04/10/2004	21,810,000.00

***** 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	422,000.00
		TOTAL : $	422,000.00

SON: CUATROCIENTOS VEINTIDOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Cdlo 07612-841-0065

580

SUPERINDUSTRIA Y COMERCIO

Radicacion 04105799 00000000 Folios 579
Fecha (AMD) 2004 10-21 16 54 58
Tramite 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN ✓ MODELO DE UTILIDAD	( )	(✓
Indicacion de que se solicita la concesion de una patente	( )	(✓
Datos de identificación del solicitante o de la persona que se presenta la solicitud	( )	(✓
Descripción de la invención	( )	(✓
Dibujos de ser estos pertinentes	( )	(✓
Comprobante de Pago de las tasas establecidas		
COMPLETA ( ) INCOMPLETA	( )	( )
DISEÑO INDUSTRIAL ( )		
- **Indicacion de que se solicita el registro de Diseño Industrial**	( )	( )
- **Datos de identificación del solicitante o de la persona que presenta**	( )	( )
- **la solicitud**		
- **Representación gráfica o fotografica del Diseno Industrial o muestra del**		
Material que incorpora el diseño	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )
ESQUEMA DE TRAZADO ( )		
- **Indicación de que solicita el registro de un Esquema de trazado**	( )	( )
- **Datos de identificación del solicitante o de la persona que presenta**		
La solicitud	( )	( )
Representacion grafica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )

Firma Responsable Claudia M Neva

Fecha

Industria y Comercio
SUPERINTENDENCIA

581

2020

Bogotá D C

Doctor(a)
EMILIO FERRERO
Apoderado
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

Oficio N° 10498

ASUNTO:

Radicación N°	**04-105799**
Solicitud internacional	**PCT/US03/08901**
Fecha inicio fase nacional	**2004-10-26**
Trámite	011
Evento	379
Actuación	430
Folios	001

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

- La solicitud no contiene copia del documento en que consta la cesión del derecho de patente del inventor al solicitante o a su causante (Art. 26-k) Decisión 486).

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha, 12 NOV. 2004
202063


12 NOV/04