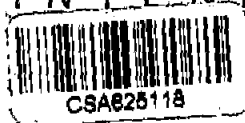




Industria y Comercio

SUPERINTENDENCIA

Organización y
Digitalización CSA Ltda



Delegatura de Propiedad Industrial

División de Nuevas Creaciones



SOLICITUD

PATENTE DE INVENCION

08-7939

21. EXPEDIENTE No.

54. TÍTULO

MÉTODOS PARA PREVENIR Y TRATAR TRASTORNOS METABÓLICOS Y NUEVOS
DERIVADOS DE PIRAZOL-O-GLUCOSIDO

51. CLASIFICACIÓN INTERNACIONAL

71. SOLICITANTE

BOEHRINGER INGELHEIM INTERNATIONAL GMRH

DOMICILIO

INGELHEIM AM RHEIN, ALEMANIA

74. APODERADO

EMILIO FERERO

C.C. 438.019 de Usaquén

22. BOGOTÁ, D. C.,

**Industria y Comercio**

SUPERINTENDENCIA

PETITORIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-007939- -00000-0000

Fecha: 2008-01-28 16:58:22

Dep. 2020 NUECREACIONI

Tra. 11 PATENTEIYII

Eve: 378 FASENACIONALI

Act. 411 PRESENTACION

Folios: 220

**FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL****SOLICITUD DE:****1**☒ Patente de Invención.☐ Patente de Modelo de Utilidad.☒ Capítulo I.☐ Capítulo II.**2****SOLICITANTE
(71)**Nombre: **BOEHRINGER INGELHEIN
INTERNATIONAL GMBH**
sociedad constituida y existente bajo las
leyes de Alemania.Dirección: 55216 Ingelheim am Rhein,
AlemaniaDomicilio: Ingelheim am Rhein,
Alemania**IDENTIFICACIÓN**

C.C.

☐

NIT

☐

C.E.

☐

Otro

☐

Cual

Número

3**REPRESENTANTE
O APODERADO**Nombre: **EMILIO FERRERO**
Dirección: Carrera 4ª. No. 72-35
Teléfono: 347 36 11
Fax: 211 86 50
E-mail: clientes@cavelier.com
Domicilio: Bogotá, Colombia.**IDENTIFICACIÓN**

C.C.

☒

NIT

☐

C.E.

☐

Otro

☐

Cual

Número 438.019 T.P 31.929**4****INVENTOR (ES)
(72)****1. Frank HIMMELSBACH**
Ahornweg 16,
88441 Mittelbiberach,
Alemania**3. Peter EICKELMANN**
Nelkenweg 9,
88441 Mittelbiberach,
Alemania**5. Edward Leon BARSOUMIAN**
18640 Maude Ave.,
Saratoga,
95070 California,
Estados Unidos de América**7. Sabine PINNETTI**
Fanny Hensel Str. 4,
88400 Biberach,
Alemania**9. Ruediger STREICHER**
Kastanienweg 31,
88400 Biberach,
Alemania**2. Roland MAIER**
Bodelschwinghstr. 39,
88400 Biberach,
Alemania**4. Leo THOMAS**
Hühnerfeldstr. 46,
88400 Biberach,
Alemania**6. Klaus DUGI**
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01309 Dresden,
Alemania**8. Regine RITTER**
Wilhelm-Kalle-Str. 2,
65203 Wiesbaden,
Alemania**10. Koichi FUJITA**
1-2-2-C1103, Shinkoyasu,
Kanagawa-Ku, Yokohama,
Kanagawa 221-0013,
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11. Toshihiro HATANAKA

2-80-3-223, Shinmei-cho,
Saiwai-ku, Kawasaki,
Kanagawa 212-0022,
Japón

12. Nozomu ISHIDA

104 Iwai-cho,
Hodogaya-ku, Yokohama,
Kanagawa 240-0023,
Japón

13. Katsumi MAEZONO

3-1-15 Yuigahama,
Kamakura,
Kanagawa 248-0014,
Japón

14. Koji OHSUMI

c/o Ajinomoto Company Apartment A110,
Ogura 811,
Saiwai-ku, Kawasaki,
Kanagawa 212-0054,
Japón

5

PCT (86)Solicitud Internacional No. PCT/EP2006/064715Fecha: 27 de julio de 2006Publicación Internacional No. WO 2007/014895 A3Fecha: 8 de febrero de 2007

6

Título (54)

**METODOS PARA PREVENIR Y TRATAR TRASTORNOS METABOLICOS Y
NUEVOS DERIVADOS DE PIRAZOL-O-GLUCOSIDO**

7

Clasificación Internacional (51) A61K 31/7056

8

PrioridadSI ☒ NO ☐

(33) País de Origen

EP

(32) Fecha

28 de julio de 2005

(31) Número de Solicitud

05016390.6

9

Comprobante de pago No.: 08-1,695**Fecha: 8 de enero de 2008**

10

Anexos:

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por \$ 501.000.00.
- ☐ 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: VER HOJA DE DOCUMENTOS ANEXOS

DOCUMENTOS ANEXOS

1. ☒ **Publicación Internacional WO 2007/014895 A3**

Descripción:

Páginas 84 en el idioma original

Páginas 83 en español

Reivindicaciones: Número (s) 22

Figuras: Número (s)

2. ☒ **Forma PCT/ISA/210**. Informe de Búsqueda Internacional.
3. ☒ **Forma PCT/ISA/237**. Opinión Escrita De La Administración Encargada De La Búsqueda Internacional.
4. ☒ **Forma PCT/IB/306**. Notificación de la inscripción del cambio de dirección del inventor **Leo THOMAS**
5. ☒ Extracto de publicación.

**NO SE REALIZARON MODIFICACIONES EN LA
FASE INTERNACIONAL**



CONSULADO GENERAL DE COLOMBIA

MUNICH

Nr. 169

El Cónsul General de Colombia

C E R T I F I C A

Que el Dr. Hanns Paul Tüttenberg -----, quién autentica la firma del signatario en el presente documento, ejercía en la fecha allí indicada las funciones de Presidente del Tribunal Regional -en Mainz. -----

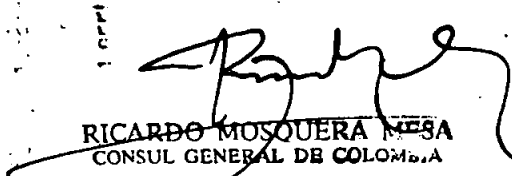
Que la firma BOEHRINGER INGELHEIM INTERNATIONAL GmbH, domiciliada en 55216 Ingelheim am Rhein, Registro Mercantil Nr. HR B 1063 del Juzgado Municipal de Bingen ----- está constituida y ejerce su objeto social de conformidad con las leyes de la República Federal de Alemania.

Que los señores Dr. DIETER LAUDIN y Dr. GERHARD HUBER -----

quien(es) firman el presente documento tiene(n) facultad legal suficiente para representar a la mencionada firma y otorgar poderes en su nombre.

Que ha tenido a la vista la documentación que prueba lo anterior.

Munich, 18 de Diciembre de 1995


RICARDO MOSQUERA MESA
CONSUL GENERAL DE COLOMBIA



Derechos para la Nación	US \$	6.-
Fondo Rotatorio	US \$	100.-
Tasa consular	US \$	1 x DM 1,60 = DM 169.60

PAGADO



BOGOTIN 621 10081471



COPIA FIDEL
DOCUMENTO DE
LAS FUNCIONES INDICA

MINISTERIO DE RELACIONES
EXTERIORES

[Signature]
05/11/08

DEPTO DE LEGALIZACIONES
BOGOTA D.C.

11:44

NO SE ASUME
RESPONSABILIDAD DEL FEALTO

COMO NOTARIO SEXTO(E) DEL CIRCULO
DE BOGOTA, HAGO CONSTAR QUE LA
FOTOCOPIA COINCIDE CON EL ORIGINAL
QUE HE TENIDO A LA VISTA
24 FEB 2008



1-04-5133
Cuz Arriaga
Resolución No. 57

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

9253
0569

I (we), the undersigned / Yo (nosotros), abajo firmado (s)
BOEHRINGER INGELHEIM INTERNATIONAL GMBH

of/domiciliado (s) en D-55216 Ingelheim am Rhein,
GERMANY

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 N° 72-35, Bogotá, Colombia, en obediencia a lo dispuesto en el parágrafo 1º del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, o 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 N° 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 mentioned matters, they may substitute this Power of Attorney, compromise, conciliate, admit facts of the case, desist, cancel, receive, renounce, and ratify acts done by representatives with the power of attorney.

Given and signed this/Dado y firmado hoy
BOEHRINGER INGELHEIM
INTERNATIONAL GMBH

In/en ppq.

Dr. Dieter Laudien
Signature

Dr. Gerhard Huber
Firma

24 FNE 2000
Ingelheim am Rhein, 12.12.1995



LEGALIZACION

El Señor Cónsul de Colombia debe expedir un *certificado consular* sobre (1) la existencia legal de la compañía que otorga el poder, (2) que ésta ejerce su objeto social, y (3) que las personas que otorgan el poder están autorizadas para dárselo. A este efecto les solicitamos que muestren al Señor Cónsul las pruebas que acreditan esos hechos (1), (2) y (3).

LEGALIZATION

The Colombia Consul must issue a *consular certificate*, on (1) the legal existence of the company which grants Power-of-Attorney, (2) that it is in actual exercise of company purposes, and (3) that the persons who execute the Power of Attorney is authorized to do so. To this effect, please show the Consul the evidence to prove the above facts (1), (2) and (3).



NOTA PARA EL SEÑOR CONSUL DE COLOMBIA: Según los artículos 65 del C. de P.C. y 480 del C. de Co., si el poderdante es una sociedad, el Señor Cónsul debe certificar que tuvo a la vista las pruebas de su existencia, que ejerce su objeto social y que quien confiere el poder es su representante.

UR.Nr. 2659 / 95 V

Vorseitige, vor mir gefertigte Namensunterschriften der Herren:

1. Dr. Dieter L a u d i e n, Dipl.-Chemiker, wohnhaft in 55127 Mainz..
2. Dr. Gerhard H u b e r, Rechtsanwalt, wohnhaft in 55411 Bingen, .

- mir bekannt -

beglaubige ich hiermit.

Gleichzeitig bescheinige ich aufgrund heutiger Einsichtnahme in das Handelsregister des Amtsgerichts Bingen, daß die Firma Boehringer Ingelheim International GmbH mit Sitz in Ingelheim am Rhein im Handelsregister des Amtsgerichts Bingen unter HR B 1063 eingetragen ist und daß die Herren Dr. Laudien und Dr. Huber als Prokuristen gemeinschaftlich zur Vertretung der Gesellschaft berechtigt sind.

Ingelheim am Rhein, den 12. Dezember 1995/hün

Notariatsverweser
anstelle des Notars
Prof. Dr. Weirich in Ingelheim



- 910 E 1 -

COMO NOTARIO SECTORIAL DEL CIRCULO
DE BOGOTA, HAGO CONSTAR QUE LA
FOTOCOPIA COINCIDE CON EL ORIGINAL
QUE HE TENIDO A LA VISTA.
24 ENE. 2008

Die Echtheit vorstehender Unterschrift des Notarassessors
Dr. Peter Wirth - Notariatsverweser anstelle des Notars
Prof. Dr. Weirich in Ingelheim und die Echtheit des bei-
gedruckten Dienst - ~~scheins~~ - siegels werden hierdurch
bestätigt. Zugleich wird bescheinigt, daß der Vorgenannte
zur Vornahme der Amtshandlung gesetzlich befugt war.

Kostenberechnung:
Gebühr für Legalisa-
tion
(Wert: DM 5000,-)
JV KostO. v. 26.7.1987
BGBl. I S. 851
DM 20,-

Mainz, den 13. DEZ. 1995

Amtsleiter



Mainz, den dreizehnen Dezember neunzehnhundertfünfundneunzig
Der Präsident des Landgerichts

Dr. Hans Paul Tüllenberg

89

TRADUCCION OFICIAL No. 5133

de un documento escrito en Alemán, el cual para su identificación se sella con el sello de la traductora, lo mismo que la presente.-

(A continuación del poder conferido a GERMAN CAVELIER, tpa. 832; GONZALO PERDOMO, tpa. 831; EMILIO FERRERO tpa, 31929; y LUZ CLEMENCIA DE PAEZ, tpa 23555; domiciliados en la Carrera 4 No. 72-35, Bogotá, Colombia, por la BOEHRINGER INGELHEIM INTERNATIONAL GMBH, domiciliada en D-55216 Ingelheim am Rhein, RFA, a través de sus representantes los Srs. Dr. Dieter Laudien y Dr. Gerhard Huber:)

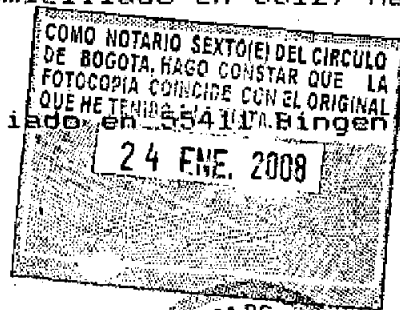
Legalización

Protocolo notarial No. 2659/95 V

Certifico la autenticidad de las firmas antecedentes puestas ante mí por los señores:

1. Dr. Dieter Laudien, Dipl. Chim., domiciliado en 55127 Mainz,
2. Dr. Gerhard Huber, abogado, domiciliado en 55411 Bingen

a quienes conozco en persona.



LUZ ANGLADA DE PERDOMO
TRADUCTORA
Fotocopia
Resolución No. 599 Minutaria

Igualmente certifico, por haber examinado en la fecha el Registro de Comercio del Juzgado Municipal de Bingen, HR B 1063, que la firma Boehringer Ingelheim International GmbH, domiciliada en Ingelheim am Rhein, está inscrita bajo el No. HR B 1063 en el Registro de Comercio del Juzgado Municipal de Bingen y que los señores Dr. Laudien y Dr. Huber, en su calidad de apoderados, están facultados para representar conjuntamente a la sociedad.

Ingelheim am Rhein, 12 de diciembre de 1995/hün

Fdo.: firma ilegible

(Hilo y oblea roja en relieve:.) El notario suplente

El notario suplente - Ingelheim del notario de Ingelheim

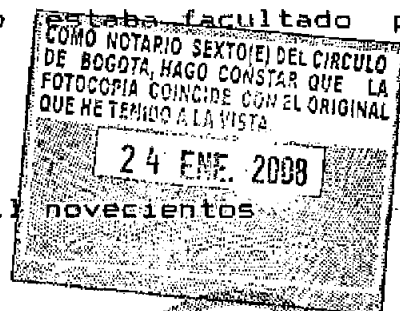
Prof. Dr. Weirich

(dos sellos redondos en tinta del Tribunal Regional de Mainz)

910 E 1

Se certifica la autenticidad de la firma antecedente del Dr. Peter Wirth, como notario suplente del Prof. Dr. Weirich, notario de Ingelheim, y la del sello oficial que la acompaña. Igualmente se certifica que el mencionado notario estaba facultado para realizar ese acto oficial.

Mainz, trece de diciembre de mil novecientos
noventa y cinco



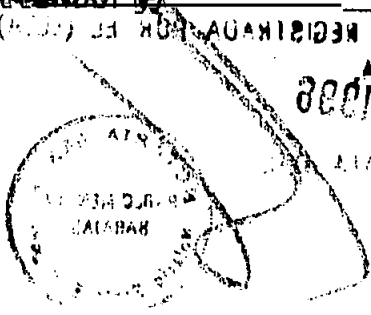
COMO NOTARIO SEXTO ENCARGADO DE SANTAFE
DE BOGOTA, HAGO CONSTAR QUE LA FIRMA DE
El Presidente del Tribunal Regional

(E) Fdo.: firma ilegible

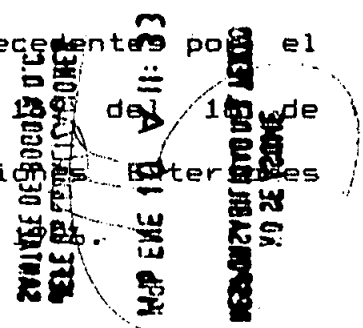
(Dr. Hanns Paul Tübbenberg)
COINCIDE CON LA REGISTRO EN ESTA NOTARIA

Costas

Derechos de legalización
(Valor:DM 5.000,--)
JVKostO del 26 de julio 1957
Gacetas Oficial I Pag. 861
DM 20,--
Mainz, 13 de diciembre de 1995
Fdo.: firma ilegible
Inspector



EN ESPAÑOL: La legalización de las firmas antecedentes por el
Consulado de Colombia en Munich bajo el No. 1 de 1 de
diciembre de 1995, y por el Ministerio de Relaciones Exteriores
de Colombia bajo el No. 051606 del 4 de enero de 1996.
Pagados derechos y Fondo Rotatorio US\$ 106,--



ES TRADUCCION FIEL Y COMPLETA, de la cual se deja copia en los
archivos de estas oficinas para su confrontación.

Santafé de Bogotá, 6 de enero de 1996.

LUZ ARRIAGA DE HERBER
TRADUCTORA E INTERPRETE OFICIAL

COMO NOTARIO SEXTO(E) DEL CREGO
DE BOGOTA, HAGO CONSTAR QUE LA
FOTOCOPIA COINCIDE CON EL ORIGINAL
QUE HE TENIDO A LA VISTA.
24 ENE. 2008



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

09 ENE 1996

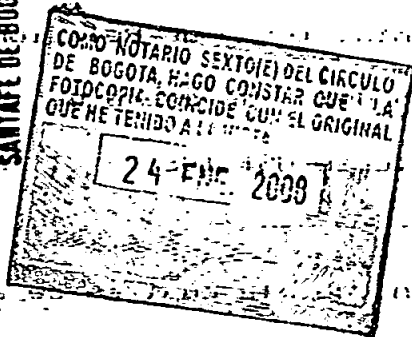
SANTAFE DE BOGOTA D.C.



NO SE ASUME
RESPONSABILIDAD DEL VERO

09 ENE 10 A 11:33

JEFE DE ADMINISTRACIONES
SANTAFE DE BOGOTA D.C.



MINISTERIO DE RELACIONES
EXTERIORES

CUYA FIRMA COINCIDE CON LA
REGISTRADA EN LA
LAS FUNCIONES DE NOTARIO



TELEFAX: (57) (1) 371 9850
TELEX: 45479 CAVE CO
1231740 7375 CAVE UC

CAVELIER

ABOGADOS

EDIFICIO SISKI
CARRERA 49, No. 72-35
BOGOTA 8, COLOMBIA

CORREO ELECTRONICO MUNDIAL: CAVE
TELEFONO (57) (1) 2120100
CABLES: CAVELEYES

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

Poderdante: BOEHRINGER INGELHEIM INTERNATIONAL GMBH

Poder conferido el: 12-12-95.

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.

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

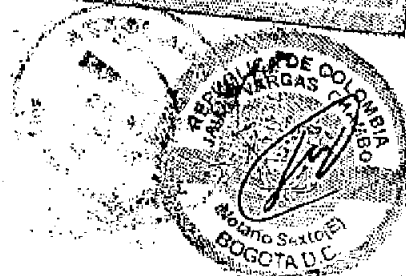
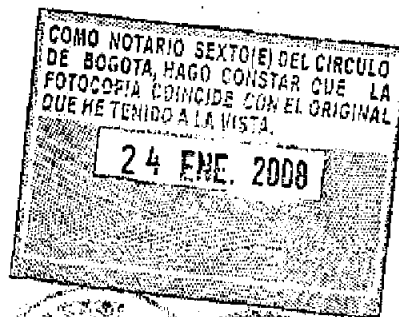
C.C. No. 2.877.924 de Bogotá

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

Bogotá, D. C.

11 ENF 1996

Ante M. PABLO MENDEZ BARAJAS S.

NOTARIO SEXTO ENCARGADO DEL CIRCULO DE BOGOTA

Compareció(eron)

quien(es) exhibió(aron) la(s)

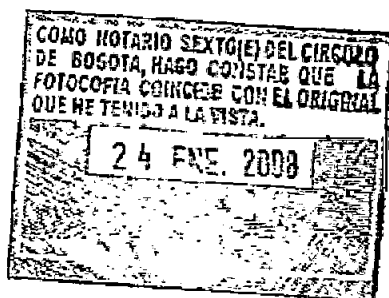
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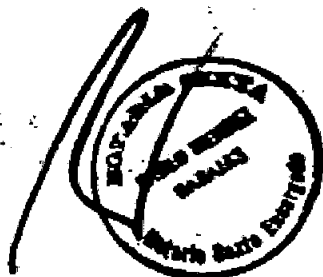
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(54) Title: METHODS FOR PREVENTING AND TREATING METABOLIC DISORDERS AND NEW PYRAZOLE-O-GLY-
COSIDE DERIVATIVES

(57) Abstract: The invention relates to methods for preventing or treating metabolic disorders, for improving glycemic control, for preventing progression from impaired glucose tolerance, insulin resistance and/or from metabolic syndrome to type 2 diabetes mellitus, for preventing or treating of complications of diabetes mellitus, for reducing the weight, for preventing or treating the degeneration of pancreatic beta cells, for treating hyperinsulinemia and insulin resistance and diabetes type 1, in patients in need thereof by administering a pharmaceutical composition comprising a pyrazole-O-glycoside as defined in claim 1, or a prodrug thereof, or a pharmaceutically acceptable salt thereof.

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**Methods for preventing and treating metabolic disorders and
new pyrazole-O-glycoside derivatives**

Technical Field of the Invention

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The invention relates to methods

- for preventing, slowing progression of, delaying, or treating a metabolic disorder;
- for improving glycemic control and/or for reducing of fasting plasma glucose, of postprandial plasma glucose and/or of glycosylated hemoglobin HbA1c;
- 10 - for preventing, slowing, delaying or reversing progression from impaired glucose tolerance, insulin resistance and/or from metabolic syndrome to type 2 diabetes mellitus;
- for preventing, slowing progression of, delaying or treating of a condition or disorder selected from the group consisting of complications of diabetes mellitus;
- for reducing the weight or preventing an increase of the weight or facilitating a reduction of the weight;
- 15 - for preventing or treating the degeneration of pancreatic beta cells and/or for improving and/or restoring the functionality of pancreatic beta cells and/or restoring the functionality of pancreatic insulin secretion;
- maintaining and/or improving the insulin sensitivity and/or for treating or preventing hyperinsulinemia and/or insulin resistance,
- 20

in patients in need thereof by administering a pharmaceutical composition comprising a pyrazole-O-glucoside derivative selected from the group of compounds (1) to (29) as defined hereinafter, or a prodrug thereof, or a pharmaceutically acceptable salt thereof. In addition the present invention relates to the use of a pyrazole-O-glucoside derivative according to this invention for preparing a pharmaceutical composition and to such medicaments and pharmaceutical compositions.

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Furthermore the present invention relates to new pyrazole-O-glucoside derivatives as defined hereinafter, or prodrugs thereof, or pharmaceutically acceptable salts thereof.

30

The present invention also relates to pharmaceutical compositions comprising at least one of the pyrazole-O-glucoside derivatives as defined hereinafter, or prodrugs thereof, or pharmaceutically acceptable salts thereof.

Background of the Invention

The European Patent application EP 1 338 603 A1 describes novel pyrazole-O-glycoside derivatives. The pyrazole-O-glycoside derivatives are proposed as inducers of urinary sugar excretion and as medicaments in the treatment of diabetes.

Renal filtration and reuptake of glucose contributes, among other mechanisms, to the steady state plasma glucose concentration and can therefore serve as an antidiabetic target. Reuptake of filtered glucose across epithelial cells of the kidney proceeds via sodium-dependent glucose cotransporters (SGLTs) located in the brush-border membranes in the proximal tubuli along the sodium gradient ⁽¹⁾. There are at least 3 SGLT isoforms that differ in their expression pattern as well as in their physico-chemical properties ⁽²⁾. SGLT2 is exclusively expressed in the kidney ⁽³⁾, whereas SGLT1 is expressed additionally in other tissues like intestine, colon, skeletal and cardiac muscle ^(4,5). SGLT3 has been found to be a glucose sensor in interstitial cells of the intestine without any transport function ⁽⁶⁾. Potentially, other related, but not yet characterized genes, may contribute further to renal glucose reuptake ^(7,8,9). Under normoglycemia, glucose is completely reabsorbed by SGLTs in the kidney, whereas the reuptake capacity of the kidney is saturated at glucose concentrations higher than 10mM, resulting in glucosuria ("diabetes mellitus"). This threshold concentration can be decreased by SGLT2-inhibition. It has been shown in experiments with the SGLT inhibitor phlorizin that SGLT-inhibition will partially inhibit the reuptake of glucose from the glomerular filtrate into the blood leading to a decrease in blood glucose concentrations and to glucosuria ^(10,11).

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15 Type 2 diabetes is an increasingly prevalent disease that due to a high frequency of complications leads to a significant reduction of life expectancy. Because of diabetes-associated microvascular complications, type 2 diabetes is currently the most frequent cause of adult-onset loss of vision, renal failure, and amputations in the industrialized world. In addition, the presence of type 2 diabetes is associated with a two to five fold increase in cardiovascular disease risk.

10 After long duration of disease, most patients with type 2 diabetes will eventually fail on oral therapy and become insulin dependent with the necessity for daily injections and multiple daily glucose measurements.

15 The UKPDS (United Kingdom Prospective Diabetes Study) demonstrated that intensive treatment with metformin, sulfonylureas or insulin resulted in only a limited improvement of glycemic control (difference in HbA1c ~0.9%). In addition, even in patients within the intensive treatment arm glycemic control deteriorated significantly over time and this was attributed to deterioration of β -cell function. Importantly, intensive treatment was not associated with a significant reduction in macrovascular complications, i.e. cardiovascular events.

20 Therefore there is an unmet medical need for drugs with a good efficacy with regard to glycemic control, with regard to disease-modifying properties and with regard to reduction of cardiovascular morbidity and mortality while at the same time showing an improved safety profile.

25 **Aim of the present invention**

The aim of the present invention is to provide a method for preventing, slowing progression of, delaying or treating a metabolic disorder.

30 A further aim of the present invention is to provide a method for improving glycemic control in a patient in need thereof.

35 Another aim of the present invention is to provide a method for preventing, slowing or delaying progression from impaired glucose tolerance, insulin resistance and/or metabolic syndrome to type 2 diabetes mellitus.

Yet another aim of the present invention is to provide a method for preventing, slowing progression of, delaying or treating of a condition or disorder from the group consisting of complications of diabetes mellitus.

- 5 A further aim of the present invention is to provide a method for reducing the weight or preventing an increase of the weight in a patient in need thereof.

Further aims of the present invention relate to new uses of pyrazole-O-glucoside derivatives according to this invention, including prodrugs and pharmaceutically acceptable salts thereof.

10

Another aim of the present invention is to provide new pyrazole-O-glucoside derivatives and new prodrugs of pyrazole-O-glucoside derivatives thereof which have a good to very good inhibitory effect on the sodium-dependent glucose cotransporter SGLT, in particular SGLT2, *in vitro* and/or *in vivo* and/or have good to very good pharmacological and/or

- 15 pharmacokinetic and/or physicochemical properties.

Further aims of the present invention become apparent to the one skilled in the art by description hereinbefore and in the following and by the examples.

20

Summary of the Invention

Within the scope of the present invention it has now surprisingly been found that a pyrazole-O-glucoside derivative selected from the group of compounds (1) to (29), or prodrugs thereof, or pharmaceutically acceptable salts thereof, as defined hereinafter can advantageously be used in preventing, slowing progression of, delaying or treating a metabolic disorder, in particular in improving glycemic control in patients. This opens up new therapeutic possibilities in the treatment and prevention of type 2 diabetes mellitus, overweight, obesity, complications of diabetes mellitus and of neighboring disease states.

30

Therefore in a first aspect the present invention provides a method for preventing, slowing progression of, delaying or treating a metabolic disorder selected from the group consisting of type 1 diabetes mellitus, type 2 diabetes mellitus, impaired glucose tolerance, hyperglycemia, postprandial hyperglycemia, overweight, obesity, including class I obesity, class II obesity, class III obesity, visceral obesity and abdominal obesity, and metabolic syndrome in a patient in need thereof characterized in that a pharmaceutical composition

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comprising a pyrazole-O-glucoside derivative selected from the group of compounds (1) to (29) consisting of

- (1) 4-(2,3-difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (2) 4-(2,5-difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (3) 4-(2,6-difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (4) 4-(3,5-difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (5) 1-cyclobutyl-4-(3-fluoro-4-methyl-benzyl)-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (6) 1-cyclopropylmethyl-4-(3-fluoro-4-methyl-benzyl)-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (7) 1-cyclobutyl-4-(2-fluoro-4-methoxy-benzyl)-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (8) 4-(3-chloro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (9) 4-(2-chloro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (10) 4-(4-bromo-3-fluoro-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (11) 4-(2,3-difluoro-4-methyl-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (12) 4-(2-fluoro-4-methyl-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (13) 4-(3-fluoro-4-ethoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (14) 4-(4-ethinyl-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (15) 4-(3-fluoro-4-isopropoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (16) 4-(2-fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;

- (17) 4-(2-fluoro-4-methoxy-benzyl)-1-isopropyl-5-trifluoromethyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (18) 4-(4-bromo-2-fluoro-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (19) 4-(2-fluoro-4-isopropoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (20) 4-(2-fluoro-4-ethoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (21) 4-(4-ethyl-benzyl)-1-isopropyl-5-trifluoromethyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (22) 4-(4-bromo-benzyl)-1-isopropyl-5-trifluoromethyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (23) 4-(4-ethyl-benzyl)-1-cyclobutyl-5-trifluoromethyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (24) 4-(4-ethyl-benzyl)-1-(2-fluoro-1-fluoromethyl-ethyl)-5-trifluoromethyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (25) 4-(3-fluoro-4-methoxy-benzyl)-1-isopropyl-5-trifluoromethyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (26) 4-(3-fluoro-4-methyl-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (27) 4-(2,3-difluoro-4-isopropoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (28) 4-(3-fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (29) 4-(4-ethyl-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;

or a prodrug thereof wherein one or more hydroxyl groups of the β-D-glucopyranosyl group are acylated with groups selected from (C₁₋₁₈-alkyl)carbonyl, (C₁₋₁₈-alkyl)oxycarbonyl, phenylcarbonyl, phenyl-(C₁₋₃-alkyl)-carbonyl, phenyloxycarbonyl and phenyl-(C₁₋₃-alkyl)-oxycarbonyl, or a pharmaceutically acceptable salt thereof;

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is administered.

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According to another aspect of the invention there is provided a method for improving glycemic control and/or for reducing of fasting plasma glucose, of postprandial plasma glucose and/or of glycosylated hemoglobin HbA1c in a patient in need thereof characterized in that a pharmaceutical composition comprising a pyrazole-O-glucoside derivative selected

5 from the group of compounds (1) to (29), or a prodrug thereof, or a pharmaceutically acceptable salt thereof, defined as hereinbefore and hereinafter is administered.

As by the use of a compound according to this invention an improvement of the glycemic control in patients in need thereof is obtainable, also those conditions and/or diseases

10 related to or caused by an increased blood glucose level may be treated.

Therefore in another aspect the invention provides a method for preventing, slowing progression of, delaying or treating of a condition or disorder selected from the group consisting of complications of diabetes mellitus such as cataracts and micro- and

15 macrovascular diseases, such as nephropathy, retinopathy, neuropathy, tissue ischaemia, arteriosclerosis, myocardial infarction, stroke and peripheral arterial occlusive disease, in a patient in need thereof characterized in that a pharmaceutical composition comprising a pyrazole-O-glucoside derivative selected from the group of compounds (1) to (29), or a prodrug thereof, or a pharmaceutically acceptable salt thereof, defined as hereinbefore and

20 hereinafter is administered. The term "tissue ischaemia" particularly comprises diabetic macroangiopathy, diabetic microangiopathy, impaired wound healing and diabetic ulcer.

The compounds according to this invention may also have valuable disease-modifying properties with respect to diseases or conditions related to impaired glucose tolerance,

25 insulin resistance and/or metabolic syndrome.

Therefore in another aspect of the present invention there is provided a method for preventing, slowing, delaying or reversing progression from impaired glucose tolerance, insulin resistance and/or from metabolic syndrome to type 2 diabetes mellitus in a patient in

30 need thereof characterized in that a pharmaceutical composition comprising a pyrazole-O-glucoside derivative selected from the group of compounds (1) to (29), or a prodrug thereof, or a pharmaceutically acceptable salt thereof, defined as hereinbefore and hereinafter is administered.

By the administration of a compound according to this invention excessive blood glucose levels are not converted to insoluble storage forms, like fat, but excreted through the urine of the patient. Therefore no gain in weight or even a reduction of the weight is the result.

- 5 Following this another aspect of the present invention provides a method for reducing the weight or preventing an increase of the weight or facilitating a reduction of the weight in a patient in need thereof characterized in that a pharmaceutical composition comprising a pyrazole-O-glucoside derivative selected from the group of compounds (1) to (29), or a prodrug thereof, or a pharmaceutically acceptable salt thereof, defined as hereinbefore and
10 hereinafter is administered.

- The pharmacological effect of the compounds according to this invention is independent of insulin. Therefore an improvement of the glycemic control is possible without an additional strain on the pancreatic beta cells. By an administration of a compound according to this
15 invention a beta-cell degeneration and a decline of beta-cell functionality such as for example apoptosis or necrosis of pancreatic beta cells can be delayed or prevented. Furthermore the functionality of pancreatic cells can be improved or restored, and the number and size of pancreatic beta cells increased. It may be shown that the differentiation status and hyperplasia of pancreatic beta-cells disturbed by hyperglycemia can be normalized by
20 treatment with a compound according to this invention.

- Therefore another aspect of the present invention provides a method for preventing, slowing, delaying or treating the degeneration of pancreatic beta cells and/or the decline of the functionality of pancreatic beta cells and/or for improving and/or restoring the functionality of
25 pancreatic beta cells and/or restoring the functionality of pancreatic insulin secretion in a patient in need thereof characterized in that a pharmaceutical composition comprising a pyrazole-O-glucoside derivative selected from the group of compounds (1) to (29), or a prodrug thereof, or a pharmaceutically acceptable salt thereof, defined as hereinbefore and hereinafter is administered.

- 30 As a result thereof another aspect of the present invention provides a method for maintaining and/or improving the insulin sensitivity and/or for treating or preventing hyperinsulinemia and/or insulin resistance in a patient in need thereof characterized in that a pharmaceutical composition comprising a pyrazole-O-glucoside derivative selected from the group of
35 compounds (1) to (29), or a prodrug thereof, or a pharmaceutically acceptable salt thereof, defined as hereinbefore and hereinafter is administered.

Other aspects of the present invention relate to the use of a pyrazole-O-glucoside derivative selected from the group of compounds (1) to (29), or a prodrug thereof, or a pharmaceutically acceptable salt thereof, defined as hereinbefore and hereinafter in the treatment or
5 prophylaxis of diseases or conditions as described hereinbefore and hereinafter.

Further aspects of the present invention relate to the use of a pyrazole-O-glucoside derivative selected from the group of compounds (1) to (29), or a prodrug thereof, or a pharmaceutically acceptable salt thereof, defined as hereinbefore and hereinafter for the
10 manufacture of a medicament for a therapeutic method as described hereinbefore and hereinafter.

Furthermore another aspect of the present invention relates to a medicament or pharmaceutical composition comprising a therapeutically or prophylactically effective amount
15 of a pyrazole-O-glucoside derivative selected from the group of compounds (1) to (29), or a prodrug thereof, or a pharmaceutically acceptable salt thereof, defined as hereinbefore and hereinafter for the treatment or prophylaxis of diseases or conditions as described hereinbefore and hereinafter.

20 Another aspect of the present invention relates to novel pyrazole-O-glucoside derivatives selected from the group consisting of:

- (1) 4-(2,3-difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3- β -D-glucopyranos-1-yloxy-1H-pyrazole;
- (2) 4-(2,5-difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3- β -D-glucopyranos-1-yloxy-1H-pyrazole;
- (3) 4-(2,6-difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3- β -D-glucopyranos-1-yloxy-1H-pyrazole;
- (4) 4-(3,5-difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3- β -D-glucopyranos-1-yloxy-1H-pyrazole;
- (5) 1-cyclobutyl-4-(3-fluoro-4-methyl-benzyl)-5-methyl-3- β -D-glucopyranos-1-yloxy-1H-pyrazole;
- (6) 1-cyclopropylmethyl-4-(3-fluoro-4-methyl-benzyl)-5-methyl-3- β -D-glucopyranos-1-yloxy-1H-pyrazole;
- (7) 1-cyclobutyl-4-(2-fluoro-4-methoxy-benzyl)-5-methyl-3- β -D-glucopyranos-1-

- yloxy-1H-pyrazole;
- (8) 4-(3-chloro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
 - (9) 4-(2-chloro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
 - (10) 4-(4-bromo-3-fluoro-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
 - (11) 4-(2,3-difluoro-4-methyl-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
 - (12) 4-(2-fluoro-4-methyl-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
 - (13) 4-(3-fluoro-4-ethoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
 - (14) 4-(4-ethinyl-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
 - (15) 4-(3-fluoro-4-isopropoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
 - (17) 4-(2-fluoro-4-methoxy-benzyl)-1-isopropyl-5-trifluoromethyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
 - (18) 4-(4-bromo-2-fluoro-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
 - (19) 4-(2-fluoro-4-isopropoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
 - (20) 4-(2-fluoro-4-ethoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;

or a prodrug thereof wherein one or more hydroxyl groups of the β-D-glucopyranosyl group are acylated with groups selected from (C₁₋₁₈-alkyl)carbonyl, (C₁₋₁₈-alkyl)oxycarbonyl, phenylcarbonyl, phenyl-(C₁₋₃-alkyl)-carbonyl, phenyloxycarbonyl and phenyl-(C₁₋₃-alkyl)-oxycarbonyl, or a pharmaceutically acceptable salt thereof.

Yet another aspect of the present invention relates to novel prodrugs of pyrazole-O-glucoside derivatives selected from the group consisting of:

- (46) 4-(3-Fluoro-4-methyl-benzyl)-1-isopropyl-5-methyl-3-(6-O-ethoxycarbonyl-

- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (47) 4-(2-Fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (48) 4-(2-Fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-isobutyloxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (49) 4-(2-Fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-hex-1-yloxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (50) 4-(2-Fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-phenoxy carbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (51) 4-(2-Fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-benzyloxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (52) 4-(2-Fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-acetyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (53) 4-(2-Fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-propylcarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (54) 4-(2-Fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-isopropylcarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (55) 4-(2-Fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-benzylcarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (56) 4-(4-ethyl-benzyl)-1-isopropyl-5-trifluoromethyl-3-(6-O-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (57) 4-(4-bromo-benzyl)-1-isopropyl-5-trifluoromethyl-3-(6-O-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (58) 4-(4-ethyl-benzyl)-1-cyclobutyl-5-trifluoromethyl-3-(6-O-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (59) 4-(4-ethyl-benzyl)-1-(2-fluoro-1-fluoromethyl-ethyl)-5-trifluoromethyl-3-(6-O-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (60) 4-(3-fluoro-4-methoxy-benzyl)-1-isopropyl-5-trifluoromethyl-3-(6-O-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (61) 4-(4-isopropoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (62) 4-(3-fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (63) 4-(4-ethyl-benzyl)-1-isopropyl-5-methyl-3-(6-O-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;

or pharmaceutically acceptable salts thereof.

A further aspect of the present invention relates to pharmaceutical compositions comprising at least one pyrazole-O-glucoside derivative according to this invention, or a

5 pharmaceutically acceptable salt thereof.

Definitions

The term "**body mass index**" or "**BMI**" of a human patient is defined as the weight in
10 kilograms divided by the square of the height in meters, such that BMI has units of kg/m^2 .

The term "**overweight**" is defined as the condition wherein the individual has a BMI greater than or 25 kg/m^2 and less than 30 kg/m^2 . The terms "overweight" and "pre-obese" are used
15 interchangeably.

The term "**obesity**" is defined as the condition wherein the individual has a BMI equal to or greater than 30 kg/m^2 . According to a WHO definition the term obesity may be categorized as follows: the term "class I obesity" is the condition wherein the BMI is equal to or greater
20 than 30 kg/m^2 but lower than 35 kg/m^2 ; the term "class II obesity" is the condition wherein the BMI is equal to or greater than 35 kg/m^2 but lower than 40 kg/m^2 ; the term "class III obesity" is the condition wherein the BMI is equal to or greater than 40 kg/m^2 .

The term "**visceral obesity**" is defined as the condition wherein a waist-to-hip ratio of
25 greater than or equal to 1.0 in men and 0.8 in women is measured. It defines the risk for insulin resistance and the development of pre-diabetes.

The term "**abdominal obesity**" is usually defined as the condition wherein the waist circumference is > 40 inches or 102 cm in men, and is > 35 inches or 94 cm in women. With
30 regard to a Japanese ethnicity or Japanese patients abdominal obesity may be defined as waist circumference ≥ 85 cm in men and ≥ 90 cm in women (see e.g. investigating committee for the diagnosis of metabolic syndrome in Japan).

The term "**euglycemia**" is defined as the condition in which a subject has a fasting blood
35 glucose concentration within the normal range, greater than 70 mg/dL (3.89

mmol/L) and less than 110 mg/dL (6.11 mmol/L). The word "fasting" has the usual meaning as a medical term.

5 The term "**hyperglycemia**" is defined as the condition in which a subject has a fasting blood glucose concentration above the normal range, greater than 110 mg/dL (6.11 mmol/L). The word "fasting" has the usual meaning as a medical term.

10 The term "**postprandial hyperglycemia**" is defined as the condition in which a subject has a 2 hour postprandial blood glucose or serum glucose concentration greater than 200 mg/dL (11.11 mmol/L).

15 The term "**impaired glucose tolerance**" or "**IGT**", is defined as the condition in which a subject has a fasting blood glucose concentration or fasting serum glucose concentration greater than 110 mg/dL and less than 126 mg/dl (7.00 mmol/L), or a 2 hour postprandial blood glucose or serum glucose concentration greater than 140 mg/dl (7.78 mmol/L) and less than 200 mg/dL (11.11 mmol/L). The term impaired glucose tolerance is also intended to apply to the condition of impaired fasting glucose. The abnormal glucose tolerance, i.e. the 2 hour postprandial blood glucose or serum glucose concentration can be measured as the blood sugar level in mg of glucose per dL of plasma 2 hours after taking 75 g of glucose after a fast.

20 The term "**hyperinsulinemia**" is defined as the condition in which a subject with insulin resistance, with or without euglycemia, in which the fasting or postprandial serum or plasma insulin concentration is elevated above that of normal, lean individuals without insulin resistance, having a waist-to-hip ration < 1.0 (for men) or < 0.8 (for women).

The terms "insulin-sensitizing", "insulin resistance-improving" or "insulin resistance-lowering" are synonymous and used interchangeably.

30 The term "**insulin resistance**" is defined as a state in which circulating insulin levels in excess of the normal response to a glucose load are required to maintain the euglycemic state (Ford ES, *et al. JAMA. (2002) 287:356-9*). A method of determining insulin resistance is the euglycaemic-hyperinsulinaemic clamp test. The ratio of insulin to glucose is determined within the scope of a combined insulin-glucose infusion technique. There is found to be insulin resistance if the glucose absorption is below the 25th percentile of the background population investigated (WHO definition). Rather less laborious than the clamp test are so

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called minimal models in which, during an intravenous glucose tolerance test, the insulin and glucose concentrations in the blood are measured at fixed time intervals and from these the insulin resistance is calculated. In this method it is not possible to distinguish between hepatic and peripheral insulin resistance.

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Furthermore insulin resistance, the response of a patient with insulin resistance to therapy, insulin sensitivity and hyperinsulinemia may be quantified by assessing the "homeostasis model assessment to insulin resistance (HOMA-IR)" score, a reliable indicator of insulin resistance (Katsuki A, *et al.* Diabetes Care 2001; 24: 362-5). Further reference is made to methods for the determination of the HOMA-index for insulin sensitivity (*Matthews et al., Diabetologia* 1985, 28: 412-19), of the ratio of intact proinsulin to insulin (*Forst et al., Diabetes* 2003, 52(Suppl.1): A459) and to an euglycemic clamp study. In addition, plasma adiponectin levels can be monitored as a potential surrogate of insulin sensitivity. The estimate of insulin resistance by the homeostasis assessment model (HOMA)-IR score is calculated with the formula (Galvin P, *et al.* Diabet Med 1992;9:921-8):

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$$\text{HOMA-IR} = [\text{fasting serum insulin } (\mu\text{U/mL})] \times [\text{fasting plasma glucose}(\text{mmol/L})/22.5]$$

As a rule, other parameters are used in everyday clinical practice to assess insulin resistance. Preferably, the patient's triglyceride concentration is used, for example, as increased triglyceride levels correlate significantly with the presence of insulin resistance.

20

Patients with a predisposition for the development of IGT or type 2 diabetes are those having euglycemia with hyperinsulinemia and are by definition, insulin resistant. A typical patient with insulin resistance is usually overweight or obese. If insulin resistance can be detected this is a particularly strong indication of the presence of prediabetes. Thus, it may be that in order to maintain glucose homeostasis a person needs 2-3 times as much insulin as another person, without this having any direct pathological significance.

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The methods to investigate the **function of pancreatic beta-cells** are similar to the above methods with regard to insulin sensitivity, hyperinsulinemia or insulin resistance: An improvement of the beta-cell function can be measured for example by determining a HOMA-index for beta-cell function (*Matthews et al., Diabetologia* 1985, 28: 412-19), the ratio of intact proinsulin to insulin (*Forst et al., Diabetes* 2003, 52(Suppl.1): A459), the insulin/C-peptide secretion after an oral glucose tolerance test or a meal tolerance test, or by

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employing a hyperglycemic clamp study and/or minimal modeling after a frequently sampled intravenous glucose tolerance test (*Stumvoll et al., Eur J Clin Invest* 2001, 31: 380-81).

The term "**pre-diabetes**" is the condition wherein an individual is pre-disposed to the development of type 2 diabetes. Pre-diabetes extends the definition of impaired glucose tolerance to include individuals with a fasting blood glucose within the high normal range ≥ 100 mg/dL (J. B. Meigs, *et al. Diabetes* 2003; 52:1475-1484) and fasting hyperinsulinemia (elevated plasma insulin concentration). The scientific and medical basis for identifying pre-diabetes as a serious health threat is laid out in a Position Statement entitled "The Prevention or Delay of Type 2 Diabetes" issued jointly by the American Diabetes Association and the National Institute of Diabetes and Digestive and Kidney Diseases (*Diabetes Care* 2002; 25:742-749).

Individuals likely to have insulin resistance are those who have two or more of the following attributes: 1) overweight or obese, 2) high blood pressure, 3) hyperlipidemia, 4) one or more 1st degree relative with a diagnosis of IGT or type 2 diabetes. Insulin resistance can be confirmed in these individuals by calculating HOMA-IR score. For the purpose of this invention, insulin resistance is defined as the clinical condition in which an individual has a HOMA-IR score > 4.0 or a HOMA-IR score above the upper limit of normal as defined for the laboratory performing the glucose and insulin assays.

The term "**type 2 diabetes**" is defined as the condition in which a subject has a fasting blood glucose or serum glucose concentration greater than 125 mg/dL (6.94 mmol/L). The measurement of blood glucose values is a standard procedure in routine medical analysis. If a glucose tolerance test is carried out, the blood sugar level of a diabetic will be in excess of 200 mg of glucose per dL of plasma 2 hours after 75 g of glucose have been taken on an empty stomach. In a glucose tolerance test 75 g of glucose are administered orally to the patient being tested after 10-12 hours of fasting and the blood sugar level is recorded immediately before taking the glucose and 1 and 2 hours after taking it. In a healthy subject the blood sugar level before taking the glucose will be between 60 and 110 mg per dL of plasma, less than 200 mg per dL 1 hour after taking the glucose and less than 140 mg per dL after 2 hours. If after 2 hours the value is between 140 and 200 mg this is regarded as abnormal glucose tolerance.

The term "**late stage type 2 diabetes mellitus**" includes patients with a secondary drug failure, indication for insulin therapy and progression to micro- and macrovascular complications e.g. diabetic nephropathy, coronary heart disease (CHD).

- 5 The term "**HbA1c**" refers to the product of a non-enzymatic glycation of the haemoglobin B chain. Its determination is well known to one skilled in the art. In monitoring the treatment of diabetes mellitus the HbA1c value is of exceptional importance. As its production depends essentially on the blood sugar level and the life of the erythrocytes, the HbA1c in the sense of a "blood sugar memory" reflects the average blood sugar levels of the preceding 4-6
- 10 weeks. Diabetic patients whose HbA1c value is consistently well adjusted by intensive diabetes treatment (i.e. < 6.5 % of the total haemoglobin in the sample), are significantly better protected against diabetic microangiopathy. For example metformin on its own achieves an average improvement in the HbA1c value in the diabetic of the order of 1.0 – 1.5 %.
- 15 This reduction of the HbA1C value is not sufficient in all diabetics to achieve the desired target range of < 6.5 % and preferably < 6 % HbA1c.

The "**metabolic syndrome**", also called "syndrome X" (when used in the context of a metabolic disorder), also called the "dysmetabolic syndrome" is a syndrome complex with the cardinal feature being insulin resistance (Laaksonen DE, *et al. Am J Epidemiol*

20 2002;156:1070-7). According to the ATP III/NCEP guidelines (Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) *JAMA: Journal of the American Medical Association* (2001) 285:2486-2497), diagnosis of the metabolic syndrome is made when three or more of the following risk factors

25 are present:

1. Abdominal obesity, defined as waist circumference > 40 inches or 102 cm in men, and > 35 inches or 94 cm in women; or with regard to a Japanese ethnicity or Japanese patients defined as waist circumference $\geq$ 85 cm in men and $\geq$ 90 cm in women;
- 30 2. Triglycerides: $\geq$ 150 mg/dL
3. HDL-cholesterol < 40 mg/dL in men
4. Blood pressure $\geq$ 130/85 mm Hg (SBP $\geq$ 130 or DBP $\geq$ 85)
5. Fasting blood glucose $\geq$ 110 mg/dL

35 The NCEP definitions have been validated (Laaksonen DE, *et al. Am J Epidemiol.* (2002) 156:1070-7). Triglycerides and HDL cholesterol in the blood can also be determined by

standard methods in medical analysis and are described for example in Thomas L (Editor): "Labor und Diagnose", TH-Books Verlagsgesellschaft mbH, Frankfurt/Main, 2000.

- 5 According to a commonly used definition **hypertension** is diagnosed if the systolic blood pressure (SBP) exceeds a value of 140 mm Hg and diastolic blood pressure (DBP) exceeds a value of 90 mm Hg. If a patient is suffering from manifest diabetes it is currently recommended that the systolic blood pressure be reduced to a level below 130 mm Hg and the diastolic blood pressure be lowered to below 80 mm Hg.
- 10 The terms "prophylactically treating" and "preventing" are used interchangeably.

Detailed Description

- 15 The aspects according to the present invention, in particular the methods and uses, refer to pyrazole-O-glucoside derivatives selected from the group of compounds (1) to (29) as defined hereinbefore and hereinafter, or prodrugs thereof, or pharmaceutically acceptable salts thereof.
- 20 Preferably all hydroxyl groups are not substituted or only the hydroxyl group connected to the carbon atom at the 6th position of the β -D-glucopyranosyl group is substituted as defined. Preferred substituents are selected from among (C₁₋₃-alkyl)carbonyl, (C₁₋₆-alkyl)oxycarbonyl, phenyloxycarbonyl, benzyloxycarbonyl and benzylcarbonyl. Even more preferred substituents are selected from among acetyl, methoxycarbonyl and ethoxycarbonyl, in
- 25 particular ethoxycarbonyl.

Preferred prodrugs are selected from the group consisting of

- (30a) 4-(2,3-difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (30b) 4-(2,3-difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (31a) 4-(3-fluoro-4-ethoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (31b) 4-(3-fluoro-4-ethoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;

- (32a) 4-(3-fluoro-4-isopropoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (32b) 4-(3-fluoro-4-isopropoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (33a) 4-(2,5-difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (33b) 4-(2,5-difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (34a) 4-(2-fluoro-4-isopropoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (34b) 4-(2-fluoro-4-isopropoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (35a) 4-(2-fluoro-4-ethoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (35b) 4-(2-fluoro-4-ethoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (36a) 4-(2-fluoro-4-methoxy-benzyl)-1-isopropyl-5-trifluoromethyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (36b) 4-(2-fluoro-4-methoxy-benzyl)-1-isopropyl-5-trifluoromethyl-3-(6-O-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (37a) 4-(2,6-difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (37b) 4-(2,6-difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (38a) 4-(3,5-difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (38b) 4-(3,5-difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (39a) 1-cyclobutyl-4-(3-fluoro-4-methyl-benzyl)-5-methyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (39b) 1-cyclobutyl-4-(3-fluoro-4-methyl-benzyl)-5-methyl-3-(6-O-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (40a) 1-cyclopropylmethyl-4-(3-fluoro-4-methyl-benzyl)-5-methyl-3-(6-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (40b) 1-cyclopropylmethyl-4-(3-fluoro-4-methyl-benzyl)-5-methyl-3-(6-

- ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (41a) 1-cyclobutyl-4-(2-fluoro-4-methoxy-benzyl)-5-methyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (41b) 1-cyclobutyl-4-(2-fluoro-4-methoxy-benzyl)-5-methyl-3-(6-O-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (42a) 4-(4-bromo-3-fluoro-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (42b) 4-(4-bromo-3-fluoro-benzyl)-1-isopropyl-5-methyl-3-(6-O-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (43a) 4-(2,3-difluoro-4-methyl-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (43b) 4-(2,3-difluoro-4-methyl-benzyl)-1-isopropyl-5-methyl-3-(6-O-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (44a) 4-(4-bromo-2-fluoro-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (44b) 4-(4-bromo-2-fluoro-benzyl)-1-isopropyl-5-methyl-3-(6-O-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (45a) 4-(2-fluoro-4-methyl-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (45b) 4-(2-fluoro-4-methyl-benzyl)-1-isopropyl-5-methyl-3-(6-O-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;

or pharmaceutically acceptable salts thereof.

In addition further preferred prodrugs are selected from the group consisting of the
5 compounds (46) to (63), or pharmaceutically acceptable salts thereof, as defined hereinbefore and hereinafter.

Yet further preferred prodrugs are selected from the group consisting of the compounds (64) to (73)

- (64) 4-(3-fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (65) 4-(4-ethyl-benzyl)-1-isopropyl-5-trifluoromethyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (66) 4-(4-bromo-benzyl)-1-isopropyl-5-trifluoromethyl-3-(6-O-methoxycarbonyl- β -D-

- glucopyranos-1-yloxy)-1H-pyrazole;
- (67) 4-(4-ethyl-benzyl)-1-cyclobutyl-5-trifluoromethyl-3-(6-O-methoxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole;
- (68) 4-(4-ethyl-benzyl)-1-(2-fluoro-1-fluoromethyl-ethyl)-5-trifluoromethyl-3-(6-O-methoxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole;
- (69) 4-(3-fluoro-4-methoxy-benzyl)-1-isopropyl-5-trifluoromethyl-3-(6-O-methoxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole;
- (70) 4-(3-fluoro-4-methyl-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole;
- (71) 4-(4-isopropoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole;
- (72) 4-(2-fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole;
- (73) 4-(4-ethyl-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole;

or a pharmaceutically acceptable salt thereof.

According to a first preferred embodiment the aspects according to the present invention, in particular the methods and uses, refer to

- (1) 4-(2,3-difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;

or a prodrug thereof wherein the hydroxyl group connected to the carbon atom at the 6th position of the β-D-glucopyranosyl group is substituted with a substituent selected from among (C₁₋₃-alkyl)carbonyl, (C₁₋₆-alkyl)oxycarbonyl, phenyloxycarbonyl, benzyloxycarbonyl and benzylcarbonyl, in particular selected from among acetyl, methoxycarbonyl and ethoxycarbonyl; for example compound (30a) and (30b).

According to a second preferred embodiment the aspects according to the present invention, in particular the methods and uses, refer to

- (11) 4-(2,3-difluoro-4-methyl-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;

or a prodrug thereof wherein the hydroxyl group connected to the carbon atom at the 6th position of the β-D-glucopyranosyl group is substituted with a substituent selected from among (C₁₋₃-alkyl)carbonyl, (C₁₋₆-alkyl)oxycarbonyl, phenyloxycarbonyl, benzyloxycarbonyl

and benzylcarbonyl, in particular selected from among acetyl, methoxycarbonyl and ethoxycarbonyl; for example compound (43a) and (43b).

5 According to a third preferred embodiment the aspects according to the present invention, in particular the methods and uses, refer to

(12) 4-(2-fluoro-4-methyl-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;

or a prodrug thereof wherein the hydroxyl group connected to the carbon atom at the 6th position of the β-D-glucopyranosyl group is substituted with a substituent selected from among (C₁₋₃-alkyl)carbonyl, (C₁₋₆-alkyl)oxycarbonyl, phenyloxycarbonyl, benzyloxycarbonyl and benzylcarbonyl, in particular selected from among acetyl, methoxycarbonyl and
10 ethoxycarbonyl; for example compound (45a) and (45b).

According to a fourth preferred embodiment the aspects according to the present invention, in particular the methods and uses, refer to

(16) 4-(2-fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;

or a prodrug thereof wherein the hydroxyl group connected to the carbon atom at the 6th position of the β-D-glucopyranosyl group is substituted with a substituent selected from among (C₁₋₃-alkyl)carbonyl, (C₁₋₆-alkyl)oxycarbonyl, phenyloxycarbonyl, benzyloxycarbonyl and benzylcarbonyl, in particular selected from among acetyl, methoxycarbonyl and
15 ethoxycarbonyl; for example compound (47) and (72).

20 According to a fifth preferred embodiment the aspects according to the present invention, in particular the methods and uses, refer to

(20) 4-(2-fluoro-4-ethoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;

or a prodrug thereof wherein the hydroxyl group connected to the carbon atom at the 6th position of the β-D-glucopyranosyl group is substituted with a substituent selected from among (C₁₋₃-alkyl)carbonyl, (C₁₋₆-alkyl)oxycarbonyl, phenyloxycarbonyl, benzyloxycarbonyl and benzylcarbonyl, in particular selected from among acetyl, methoxycarbonyl and
25 ethoxycarbonyl; for example compound (35a) and (35b).

According to a sixth preferred embodiment the aspects according to the present invention, in particular the methods and uses, refer to

(26) 4-(3-fluoro-4-methyl-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;

or a prodrug thereof wherein the hydroxyl group connected to the carbon atom at the 6th position of the β-D-glucopyranosyl group is substituted with a substituent selected from among (C₁₋₃-alkyl)carbonyl, (C₁₋₆-alkyl)oxycarbonyl, phenyloxycarbonyl, benzyloxycarbonyl and benzylcarbonyl, in particular selected from among acetyl, methoxycarbonyl and ethoxycarbonyl; for example compound (46) and (70).

According to a seventh preferred embodiment the aspects according to the present invention, in particular the methods and uses, refer to

(28) 4-(3-fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;

or a prodrug thereof wherein the hydroxyl group connected to the carbon atom at the 6th position of the β-D-glucopyranosyl group is substituted with a substituent selected from among (C₁₋₃-alkyl)carbonyl, (C₁₋₆-alkyl)oxycarbonyl, phenyloxycarbonyl, benzyloxycarbonyl and benzylcarbonyl, in particular selected from among acetyl, methoxycarbonyl and ethoxycarbonyl; for example compound (62) and (64).

When this invention refers to patients requiring treatment or prevention, it relates primarily to treatment and prevention in humans, but the active substance may also be used accordingly in veterinary medicine on mammals.

Within the scope of the present invention the pharmaceutical composition comprising a pyrazole-O-glucoside derivative selected from the group of compounds (1) to (29), or a prodrug thereof, or a pharmaceutically acceptable salt thereof, is preferably administered orally. Other forms of administration are possible and described hereinafter. Furthermore the treatment and/or prophylaxis, in the following called therapy, according to this invention is preferably a monotherapy, i.e. during the time of the therapy preferably no other antidiabetic drug other than the compound according to this invention is given to the patient.

As described hereinbefore by the administration of a pyrazole-O-glucoside derivative according to this invention, or a prodrug or pharmaceutically acceptable salt thereof, excessive blood glucose is excreted through the urine of the patient, so that no gain in weight or even a reduction of the weight may result. Therefore a treatment or prophylaxis according to this invention is advantageously suitable in those patients in need of such treatment or prophylaxis who are diagnosed of one or more of the conditions selected from the group

consisting of overweight, class I obesity, class II obesity, class III obesity, visceral obesity and abdominal obesity or for those individuals in which a weight increase is contraindicated.

It was found that a pyrazole-O-glucoside derivative according to this invention, or a prodrug or pharmaceutically acceptable salt thereof, exhibits a very good efficacy with regard to glycemic control, in particular in view of a reduction of fasting plasma glucose, postprandial plasma glucose and/or glycosylated hemoglobin (HbA1c). By administering a pyrazole-O-glucoside derivative according to this invention, or a prodrug or pharmaceutically acceptable salt thereof, a reduction of HbA1c equal to or greater than preferably 0.5 %, even more preferably equal to or greater than 1.0 % can be achieved and the reduction is particularly in the range from 1.0 % to 1.5 %.

Furthermore the method according to this invention is advantageously applicable in those patients who show one, two or more of the following conditions:

- (a) a fasting blood glucose or serum glucose concentration greater than 110 mg/dL, in particular greater than 125 mg/dL;
- (b) a postprandial plasma glucose equal to or greater than 140 mg/dL;
- (c) an HbA1c value equal to or greater than 6.5 %, in particular equal to or greater than 8.0 %.

The present invention also discloses the use of a pharmaceutical composition for improving glycemic control in patients having type 2 diabetes or showing first signs of prediabetes. Thus, the invention also includes diabetes prevention. If therefore a pyrazole-O-glucoside derivative according to this invention, or a prodrug or pharmaceutically acceptable salt thereof, is used immediately to improve the glycemic control as soon as one of the above-mentioned signs of prediabetes is present, the onset of manifest type 2 diabetes mellitus can be delayed or prevented.

Furthermore the pyrazole-O-glucoside derivative according to this invention, or a prodrug or pharmaceutically acceptable salt thereof, is particularly suitable in the treatment of patients with insulin dependency, i.e. in patients who are treated or otherwise would be treated or need treatment with an insulin or a derivative of insulin or a substitute of insulin or a formulation comprising an insulin or a derivative or substitute thereof. These patients include patients with diabetes type 2 and patients with diabetes type 1.

It can be found that by using a pyrazole-O-glucoside derivative according to this invention, or a prodrug or pharmaceutically acceptable salt thereof, an improvement of the glycemic control can be achieved even in those patients who have insufficient glycemic control in particular despite treatment with one or more antidiabetic drugs, for example despite
5 maximal tolerated dose of oral monotherapy with either metformin or an antidiabetic of the class of sulphonylureas. A maximal tolerated dose with regard to metformin is for example 850 mg three times a day or any equivalent thereof. In the scope of the present invention the term "insufficient glycemic control" means a condition wherein patients show HbA1c values above 6.5 %, in particular above 8 %.

10

Therefore according to a preferred embodiment of the present invention there is provided a method for improving glycemic control and/or for reducing of fasting plasma glucose, of postprandial plasma glucose and/or of glycosylated hemoglobin HbA1c in a patient in need thereof who is diagnosed with impaired glucose tolerance, with insulin resistance, with
15 metabolic syndrome and/or with type 2 or type 1 diabetes mellitus characterized in that a pharmaceutical composition comprising a pyrazole-O-glucoside derivative according to this invention, or a prodrug or pharmaceutically acceptable salt thereof, is administered.

It was found that the lowering of the blood glucose level by the administration of a pyrazole-
20 O-glucoside derivative according to this invention, or a prodrug or pharmaceutically acceptable salt thereof, is insulin-independent. Therefore a pyrazole-O-glucoside derivative according to this invention, or a prodrug or pharmaceutically acceptable salt thereof, is particularly suitable in the treatment of patients who are diagnosed having one or more of the following conditions

- 25
- insulin resistance,
 - hyperinsulinemia,
 - pre-diabetes,
 - type 2 diabetes mellitus, particular having a late stage type 2 diabetes mellitus,
 - type 1 diabetes mellitus.

30

Furthermore a pyrazole-O-glucoside derivative according to this invention, or a prodrug or pharmaceutically acceptable salt thereof, is particularly suitable in the treatment of patients who are diagnosed having one or more of the following conditions

- 35
- (a) obesity (including class I, II and/or III obesity), visceral obesity and/or abdominal obesity,
 - (b) triglyceride blood level ≥ 150 mg/dL,

- (c) HDL-cholesterol blood level < 40 mg/dL in female patients and < 50 mg/dL in male patients,
- (d) a systolic blood pressure $\geq$ 130 mm Hg and a diastolic blood pressure $\geq$ 85 mm Hg,
- (e) a fasting blood glucose level $\geq$ 110 mg/dL.

5

It is assumed that patients diagnosed with impaired glucose tolerance, with insulin resistance and/or with metabolic syndrome suffer from an increased risk of developing a cardiovascular disease, such as for example myocardial infarction, coronary heart disease, heart insufficiency, thromboembolic events. A glycemic control according to this invention may

10 result in a reduction of the cardiovascular risks.

Pyrazole-O-glucoside derivatives according to this invention, or prodrugs or pharmaceutically acceptable salts thereof, exhibit a good safety profile. Therefore a treatment or prophylaxis according to this invention is advantageous possible in those

15 patients for which the treatment with other antidiabetic drugs, such as for example metformin, is contraindicated and/or who have an intolerance against such drugs at therapeutic doses. In particular a treatment or prophylaxis according to this invention is advantageous possible in those patients showing or having an increased risk for one or more of the following disorders: renal insufficiency or diseases, cardiac diseases, cardiac failure, hepatic diseases,

20 pulmonary diseases, catabolytic states and/or danger of lactate acidosis, or female patients being pregnant or during lactation.

Furthermore it could be found that the administration of a pyrazole-O-glucoside derivative according to this invention, or a prodrug or pharmaceutically acceptable salt thereof, results

25 in no or in a low risk of hypoglycemia. Therefore a treatment or prophylaxis according to this invention is also advantageously possible in those patients showing or having an increased risk for hypoglycemia.

Pyrazole-O-glucoside derivatives according to this invention, or prodrugs or

30 pharmaceutically acceptable salts thereof, are particularly suitable in the long term treatment or prophylaxis of the diseases and/or conditions as described hereinbefore and hereinafter, in particular in the long term glycemic control in patients with type 2 diabetes mellitus.

The term "long term" as used hereinbefore and hereinafter indicates a treatment of or

35 administration in a patient within a period of time longer than 12 weeks, preferably longer than 25 weeks, even more preferably longer than 1 year.

Therefore a particularly preferred embodiment of the present invention provides a method for oral therapy, preferably oral monotherapy, for improvement, especially long term improvement, of glycemic control in patients with type 2 diabetes mellitus, especially in
5 patients with late stage type 2 diabetes mellitus, in particular in patients additionally diagnosed of overweight, obesity (including class I, class II and/or class III obesity), visceral obesity and/or abdominal obesity.

It will be appreciated that the amount of the pyrazole-O-glucoside derivative according to this
10 invention, or the prodrug or pharmaceutically acceptable salt thereof, to be administered to the patient and required for use in treatment or prophylaxis according to the present invention will vary with the route of administration, the nature and severity of the condition for which treatment or prophylaxis is required, the age, weight and condition of the patient, concomitant medication and will be ultimately at the discretion of the attendant physician. In
15 general however the pyrazole-O-glucoside derivative according to this invention, or the prodrug or pharmaceutically acceptable salt thereof, is included in the pharmaceutical composition or dosage form in an amount sufficient to improve glycemic control in the patient to be treated.

20 The pharmaceutical composition to be administered to the patient according to a method as described hereinbefore and hereinafter preferably comprises an amount in the range from 1 mg to 1000 mg, even more preferably from 10 to 500 mg, most preferably from 50 to 500 mg of a pyrazole-O-glucoside derivative according to this invention, or a prodrug or pharmaceutically acceptable salt thereof, per day with respect to an adult patient. The above
25 specified amounts are especially preferred for oral administration. An example of a suitable pharmaceutical composition according to this invention is a tablet for oral administration comprising 200 mg of 4-(2-fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3- β -D-glucopyranos-1-yloxy-1H-pyrazole.

30 The desired dose of the pharmaceutical composition according to this invention may conveniently be presented in a single dose once daily or as divided dose administered at appropriate intervals, for example as two, three or more doses per day.

The pharmaceutical composition may be formulated for oral, rectal, nasal, topical (including
35 buccal and sublingual), transdermal, vaginal or parenteral (including intramuscular, subcutaneous and intravenous) administration in liquid or solid form or in a form suitable for

39

administration by inhalation or insufflation. The formulations may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the active compound with liquid carriers or finely divided solid carriers or both and then, if
5 necessary, shaping the product into the desired formulation.

The pharmaceutical composition may be formulated in the form of tablets, granules, fine granules, powders, capsules, caplets, soft capsules, pills, oral solutions, syrups, dry syrups, chewable tablets, troches, effervescent tablets, drops, suspension, fast dissolving tablets,
10 oral fast-dispersing tablets, etc..

The pharmaceutical composition preferably comprises one or more pharmaceutical acceptable carriers which must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

15
Pharmaceutical compositions suitable for oral administration may conveniently be presented as discrete units such as capsules, including soft gelatin capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution, a suspension or as an emulsion, for example as syrups, elixirs or self-emulsifying
20 delivery systems (SEDDS). The active ingredient may also be presented as a bolus, electuary or paste. Tablets and capsules for oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, or wetting agents. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions,
25 syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), or preservatives.

30 The pharmaceutical composition according to the invention may also be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles,
35 and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic

isolation of sterile solid or by lyophilisation from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

5 Pharmaceutical compositions suitable for rectal administration wherein the carrier is a solid are most preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art, and the suppositories may be conveniently formed by admixture of the active compound(s) with the softened or melted carrier(s) followed by chilling and shaping in moulds.

10 Examples of pharmaceutically acceptable carriers are known to the one skilled in the art.

Methods for the manufacture of pyrazole-O-glucoside derivatives according to this invention and of prodrugs thereof are known to the one skilled in the art. Advantageously the compounds according to this invention can be prepared using synthetic methods as
15 described in the literature, in particular as described in the EP 1 338 603 A1, EP 1 389 621 A1, WO 04/014932, WO 04/018491, WO 04/019958, WO 04/031203, WO 04/050122 and WO 03/020737. Preferred methods for the synthesis of the compounds according to this invention are described in the examples.

20 When the compounds according to this invention can form salts thereof, the salts should be pharmaceutically acceptable. Pharmaceutically acceptable salts include such as salts of inorganic acid like hydrochloric acid, sulfuric acid and phosphoric acid; salts of organic carboxylic acid like oxalic acid, acetic acid, citric acid, malic acid, benzoic acid, maleic acid, fumaric acid, tartaric acid, succinic acid and glutamic acid and salts of organic sulfonic acid
25 like methanesulfonic acid and p-toluenesulfonic acid. The salts can be formed by combining the compounds of this invention and an acid in the appropriate amount and ratio in a solvent and decomposer. They can be also obtained by the cation or anion exchange from the form of other salts.

30 The compounds according to this invention include solvates such as hydrates and alcohol adducts.

The biological properties of the new compounds may be investigated as it is described for example in EP 1 338 603 A1, in particular with regard to the inhibiting activity on renal brush
35 border membrane glucose uptake and to the activity on rat's sugar urine excretion. Furthermore the following tests may be applied:

41

The ability of the substances to inhibit the SGLT-2 activity may be demonstrated in a test set-up in which a CHO-K1 cell line (ATCC No. CCL 61) or alternatively an HEK293 cell line (ATCC No. CRL-1573), which is stably transfected with an expression vector pZeoSV (Invitrogen, EMBL accession number L36849), which contains the cDNA for the coding sequence of the human sodium glucose cotransporter 2 (Genbank Acc. No. NM_003041) (CHO-hSGLT2 or HEK-hSGLT2). These cell lines transport ^{14}C -labelled alpha-methyl-glucopyranoside (^{14}C -AMG, Amersham) into the interior of the cell in sodium-dependent manner.

The SGLT-2 assay is carried out as follows:

CHO-hSGLT2 cells are cultivated in Ham's F12 Medium (BioWhittaker) with 10% foetal calf serum and 250 $\mu\text{g}/\text{ml}$ zeocin (Invitrogen), and HEK293-hSGLT2 cells are cultivated in DMEM medium with 10% foetal calf serum and 250 $\mu\text{g}/\text{ml}$ zeocin (Invitrogen).

The cells are detached from the culture flasks by washing twice with PBS and subsequently treating with trypsin/EDTA. After the addition of cell culture medium the cells are centrifuged, resuspended in culture medium and counted in a Casy cell counter. Then 40,000 cells per well are seeded into a white, 96-well plate coated with poly-D-lysine and incubated overnight at 37°C , 5% CO_2 . The cells are washed twice with 250 μl of assay buffer (Hanks Balanced Salt Solution, 137 mM NaCl, 5 mM KCl, 2.8 mM CaCl_2 , 1.2 mM MgSO_4 and 10 mM HEPES (pH 7.4), 50 $\mu\text{g}/\text{ml}$ of gentamycin, 250 μl of assay buffer and 5 μl of test compound are then added to each well and the plate is incubated for a further 15 minutes in the incubator. 5 μl of 10% DMSO are used as the negative control. The reaction is started by adding 5 μl of ^{14}C -AMG (0.05 μCi) to each well. After 2 hours' incubation at 37°C , 5% CO_2 , the cells are washed again with 250 μl of PBS (20°C) and then lysed by the addition of 25 μl of 0.1 N NaOH (5 min. at 37°C). 200 μl of MicroScint20 (Packard) are added to each well and incubation is continued for a further 20 min at 37°C . After this incubation the radioactivity of the ^{14}C -AMG absorbed is measured in a Topcount (Packard) using a ^{14}C scintillation program.

To determine the selectivity with respect to human SGLT1 an analogous test is set up in which the cDNA for hSGLT1 (Genbank Acc. No. NM000343) instead of hSGLT2 cDNA is expressed in CHO-K1 or HEK293 cells.

In the foregoing and following text, H atoms of hydroxyl groups are not explicitly shown in every case in structural formulae. The Examples that follow are intended to illustrate the present invention without restricting it.

5 Examples

The following abbreviations are used above and hereinafter:

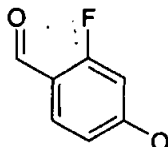
Bn	benzyl
Bu	butyl
10 DCM	dichloromethane
DMF	dimethylformamide
Et	ethyl
EtOAc	ethyl acetate
iPr	iso-propyl
15 i. vac.	in vacuo
Me	methyl
Ph	phenyl
RT	ambient temperature (approx. 20°C)
THF	tetrahydrofuran

20

Preparation of Starting Materials:

Example I

2-Fluoro-4-hydroxy-benzaldehyde



25

To a -70 °C solution of 2-fluoro-4-methoxy-benzaldehyde (19.1 g, 120 mmol) in CH₂Cl₂ (100 mL) was added boron tribromide in CH₂Cl₂ (1 M, 160 mL, 160 mmol). After stirring the reaction solution at -68 °C for 45 min the cooling bath was removed, and the solution was further stirred at room temperature over night. The reaction solution was poured into ice water and stirred for 30 min. The formed precipitate was separated, washed with CH₂Cl₂, and dissolved in EtOAc. The resultant EtOAc phase was washed with water and dried over MgSO₄. After evaporation of the solvent the residue was washed with little CH₂Cl₂ and dried *in vacuo* to give the product as a beige solid.

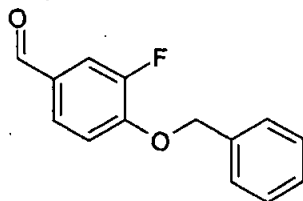
30

Yield: 14.5 g (86%)

ESI-MS: $m/z = 139$ $[M-H]^-$

5 Example II

4-Benzyloxy-3-fluoro-benzaldehyde



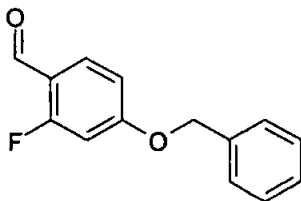
To a suspension of 4-hydroxy-3-fluoro-benzaldehyde (10.0 g, 70 mmol) and potassium carbonate (10.2 g, 74 mmol) in DMF (60 mL) was added dropwise benzyl bromide (8.7 mL, 74 mmol). The mixture was stirred at ambient temperature for 48 h and subsequently quenched with ice water. The mixture was further diluted with water, and the precipitate was separated by filtration. The precipitate was washed with water and dissolved in ethyl acetate. The organic solution was washed with brine, dried over sodium sulfate, and the solvent was removed *in vacuo*.

15 Yield: 16.0 g (99%)

ESI-MS: $m/z = 231$ $[M+H]^+$

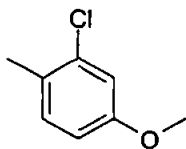
In an analogous manner the following compounds can be obtained:

20 (1) 4-Benzyloxy-2-fluoro-benzaldehyde



ESI-MS: $m/z = 253$ $[M+Na]^+$

(2) 2-Chloro-4-methoxy-1-methyl-benzene



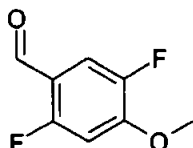
25

The procedure above was followed except for benzyl bromide methyl iodide was employed as the electrophile.

ESI-MS: $m/z = 156/158 [M]^+$ (chlorine)

5 Example III

2,5-Difluoro-4-methoxy-benzaldehyde



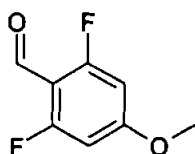
To a $-65\text{ }^{\circ}\text{C}$ solution of 1-bromo-2,5-difluoro-4-methoxy-benzene (25.0 g, 0.11 mol) in THF (150 mL) and Et_2O (250 mL) under Ar was added dropwise $n\text{-BuLi}$ in hexane (1.6 M, 70 mL, 0.11 mol). After stirring the solution at $-65\text{ }^{\circ}\text{C}$ for 45 min, DMF (10 mL, 0.13 mol) was added slowly. The solution was warmed up in the cooling bath to room temperature over night and then diluted with Et_2O (500 mL). The resultant organic solution was washed with brine, dried over MgSO_4 , and the solvent was removed *in vacuo*. The residue was recrystallized from $i\text{Pr}_2\text{O}$ to give the product as yellow crystals.

15 Yield: 6.7 g (35%)

R_f 0.63 (silica gel, petrol ether/ EtOAc 1:1)

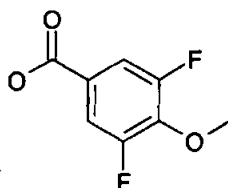
In an analogous manner the following compounds can be obtained:

20 (1) 2,6-Difluoro-4-methoxy-benzaldehyde



ESI-MS: $m/z = 173 [M+H]^+$

(2) 3,5-Difluoro-4-methoxy-benzoic acid



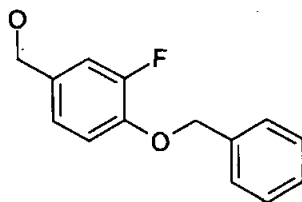
25

The procedure above was followed except for the quenching of the aryllithium compound with crushed dry ice (CO_2) instead of DMF.

ESI-MS: $m/z = 187$ $[M-H]^-$

Example IV

(4-Benzyloxy-3-fluoro-phenyl)-methanol



5

To a suspension of sodium borohydride (3.4 g, 90 mmol) in THF (60 mL) was added a solution of 4-benzyloxy-3-fluoro-benzaldehyde (16.1 g, 70 mmol) in THF (60 mL). After stirring at ambient temperature over night, the reaction mixture was quenched by the addition of ice water. The mixture was acidified with aqueous HCl (4 M) and extracted with Et₂O. The combined organic phases were washed with aqueous NaHCO₃ solution and dried over sodium sulfate. After removal of the solvent, the product was yielded.

10

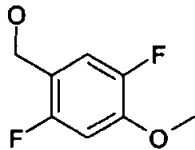
Yield: 16.2 g (100%)

ESI-MS: $m/z = 215$ $[M-OH]^+$

15

In an analogous manner the following compounds can be prepared:

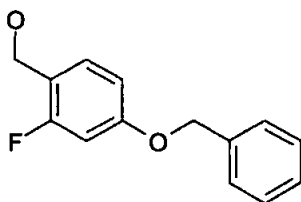
(1) (2,5-Difluoro-4-methoxy-phenyl)-methanol



ESI-MS: $m/z = 215$ $[M-OH]^+$

20

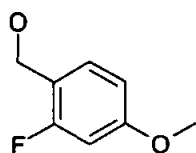
(2) (4-Benzyloxy-2-fluoro-phenyl)-methanol



ESI-MS: $m/z = 232$ $[M]^+$

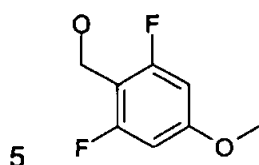
25

(3) (2-Fluoro-4-methoxy-phenyl)-methanol



ESI-MS: $m/z = 139$ $[M-OH]^+$

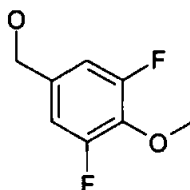
(4) (2,6-Difluoro-4-methoxy-phenyl)-methanol



ESI-MS: $m/z = 157$ $[M-OH+H]^+$

Example V

(3,5-Difluoro-4-methoxy-phenyl)-methanol



10

To a 20 °C suspension of lithium aluminumhydride (0.57 g, 15 mmol) in THF (50 mL) and toluene (30 mL) was added a solution of 3,5-difluoro-4-methoxy-benzoic acid (2.9 g, 15 mmol) in THF (20 mL). After stirring the reaction mixture at ambient temperature over night, ice water was added, and the resultant solution was acidified with 2 N sulfuric acid. The

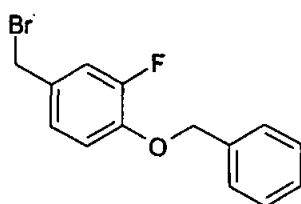
15 organic layer was separated and the aqueous extracted with EtOAc. The combined organic phases were washed with aqueous NaHCO_3 solution and brine and dried over MgSO_4 . After removal of the solvent, the residue was purified by chromatography on silica gel (petrol ether/EtOAc 2:1).

Yield: 1.6 g (60%)

20 R_f 0.7 (silica gel, petrol ether/EtOAc 1:1)

Example VI

1-Benzyloxy-4-bromomethyl-2-fluoro-benzene



To an ice-cold solution of (4-benzyloxy-3-fluoro-phenyl)-methanol (16.7 g, 72 mmol) in diethylether (130 mL) was added phosphorous tribromide (2.8 mL, 30 mmol) at a rate such that the solution temperature did not exceed 8 °C. After stirring at room temperature for 2 h, the reaction mixture was cooled in an ice-bath and quenched by the addition of ice water, ethyl acetate, and Et₂O. The organic layer was separated and washed with aqueous NaHCO₃ solution and brine. The product was yielded after evaporation of the solvent.

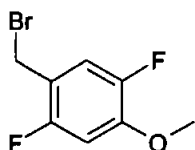
Yield: 20.5 g (97%)

ESI-MS: $m/z = 294/296$ [M]⁺ (bromine)

10

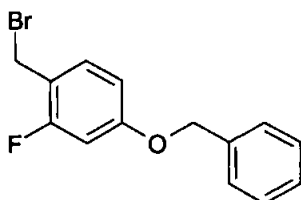
In an analogous manner the following compounds were prepared:

(1) 1-Bromomethyl-2,5-difluoro-4-methoxy-benzene



15 ESI-MS: $m/z = 236/238$ [M]⁺ (bromine)

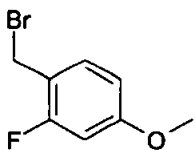
(2) 4-Benzyloxy-1-bromomethyl-2-fluoro-benzene



ESI-MS: $m/z = 294/296$ [M]⁺ (bromine)

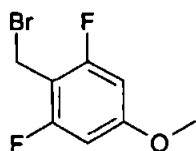
20

(3) 1-Bromomethyl-2-fluoro-4-methoxy-benzene



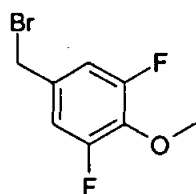
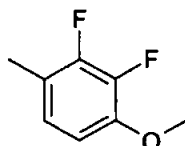
R_f 0.8 (silica gel, petrol ether/EtOAc 1:1)

(4) 2-Bromomethyl-1,3-difluoro-5-methoxy-benzene

ESI-MS: $m/z = 236/238$ $[M]^+$ (bromine)

5

(5) 5-Bromomethyl-1,3-difluoro-2-methoxy-benzene

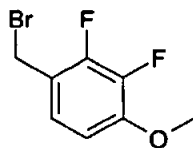
ESI-MS: $m/z = 236/238$ $[M]^+$ (bromine)10 Example VII2,3-Difluoro-1-methoxy-4-methyl-benzene

To a 20 °C solution of sodium hydroxide (14.4 g, 0.36 mol) and 2,3-difluoro-4-methyl-phenol (50.0 g, 0.35 mol) in water (160 mL) was added dropwise dimethyl sulfate (34 mL, 0.36 mol).

- 15 After stirring at room temperature over night, the reaction solution was extracted with Et₂O. The ether phase was washed with 2 N NaOH solution, water, and brine and subsequently dried over MgSO₄. After removal of the solvent under reduced pressure, the product was yielded as a colorless oil.

Yield: 49.0 g (89%)

- 20 ESI-MS: $m/z = 158$ $[M]^+$

Example VIII1-Bromomethyl-2,3-difluoro-4-methoxy-benzene

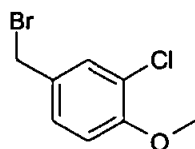
A solution of 2,3-difluoro-1-methoxy-4-methyl-benzene (39.5 g, 0.25 mol), N-bromo succinimide (44.5 g, 0.25 mol), and azobisisobutyronitrile (0.41 g, 2.5 mmol) in CCl₄ (300 mL) was stirred at reflux for 3.5 h. Then the formed succinimide was removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was dissolved in Et₂O (200 mL) and concentrated to about 100 mL. After cooling in an ice-bath the formed precipitate was filtered off, washed with cold Et₂O, and dried *in vacuo* to give the product as a white solid.

Yield: 36.0 g (61%)

R_f 0.3 (silica gel, petrol ether/EtOAc 20:1)

10 The following compounds can be obtained by analogy with the procedure described above:

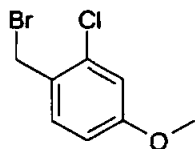
(1) 4-Bromomethyl-2-chloro-1-methoxy-benzene



R_f 0.4 (silica gel, petrol ether/EtOAc 20:1)

15

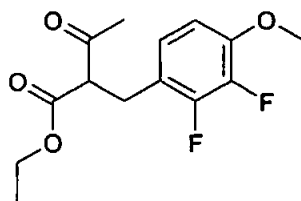
(2) 1-Bromomethyl-2-chloro-4-methoxy-benzene



R_f 0.5 (silica gel, petrol ether/EtOAc 20:1)

20 Example IX

2-(2,3-Difluoro-4-methoxy-benzyl)-3-oxo-butyric acid ethyl ester



To an ice-cold suspension of sodium hydride (4.8 g, 120 mmol, 60% in mineral oil, freed from oil with pentane) in THF (140 mL) was added 3-oxo-butyric acid ethyl ester (17.2 g, 132 mmol) in THF (50 mL). After removing the ice-bath and stirring the solution at room temperature for 0.5 h, a solution of 1-methoxy-4-bromomethyl-2,3-difluoro-benzene (28.4 g,

25

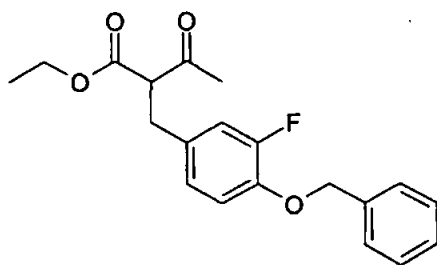
120 mmol) in THF (60 mL) was added dropwise. After stirring the reaction mixture at reflux over night, the solvent was removed *in vacuo* and the residue was triturated with Et₂O (300 mL). The ether phase was washed with water and brine and dried over MgSO₄. The product was furnished as a yellow oil after evaporation of the solvent.

5 Yield: 35.5 g (ca. 80% pure)

ESI-MS: $m/z = 285 [M-H]^-$

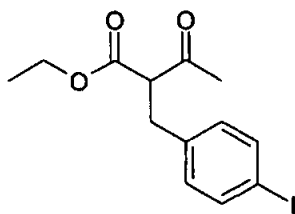
The following compounds can be obtained in an analogous manner:

10 (1) 2-(4-Benzyloxy-3-fluoro-benzyl)-3-oxo-butyric acid ethyl ester



ESI-MS: $m/z = 345 [M+H]^+$

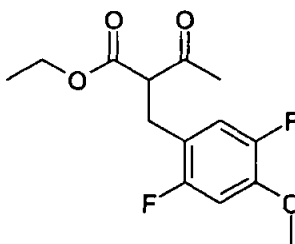
(2) 2-(4-Iodo-benzyl)-3-oxo-butyric acid ethyl ester



15

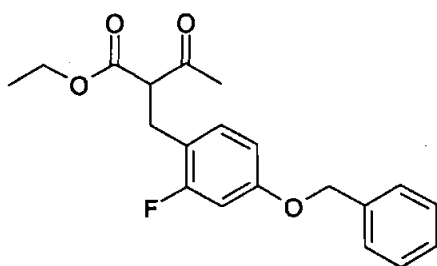
ESI-MS: $m/z = 345 [M-H]^-$

(3) 2-(2,5-Difluoro-4-methoxy-benzyl)-3-oxo-butyric acid ethyl ester



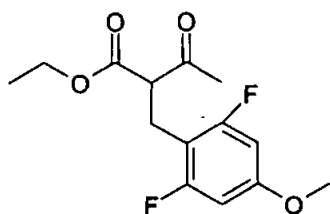
20 R_f 0.27 (silica gel, petrol ether/EtOAc 4:1)

(4) 2-(4-Benzyloxy-2-fluoro-benzyl)-3-oxo-butyric acid ethyl ester



ESI-MS: $m/z = 343 [M-H]^-$

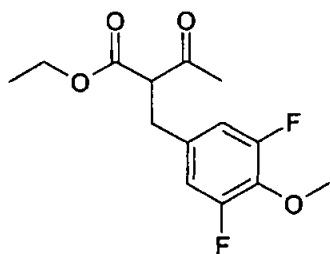
(5) 2-(2,6-Difluoro-4-methoxy-benzyl)-3-oxo-butyric acid ethyl ester



5

ESI-MS: $m/z = 287 [M+H]^+$

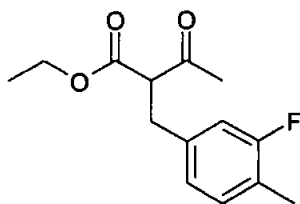
(6) 2-(3,5-Difluoro-4-methoxy-benzyl)-3-oxo-butyric acid ethyl ester



10

ESI-MS: $m/z = 287 [M+H]^+$

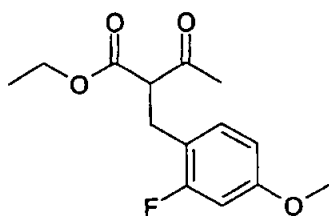
(7) 2-(3-Fluoro-4-methyl-benzyl)-3-oxo-butyric acid ethyl ester



ESI-MS: $m/z = 253 [M+H]^+$

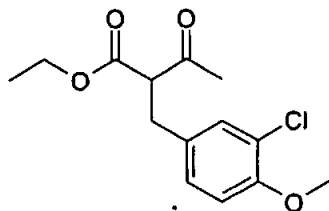
15

(8) 2-(2-Fluoro-4-methoxy-benzyl)-3-oxo-butyric acid ethyl ester



ESI-MS: $m/z = 269 [M+H]^+$

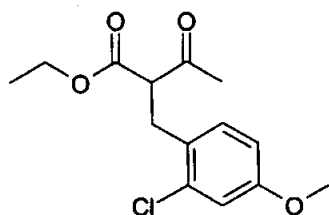
(9) 2-(3-Chloro-4-methoxy-benzyl)-3-oxo-butyric acid ethyl ester



5

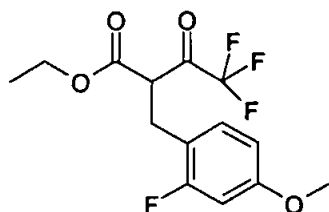
ESI-MS: $m/z = 283/285 [M-H]^-$ (chlorine)

(10) 2-(2-Chloro-4-methoxy-benzyl)-3-oxo-butyric acid ethyl ester



10 ESI-MS: $m/z = 285/287 [M+H]^+$ (chlorine)

(11) 4,4,4-Trifluoro-2-(2-fluoro-4-methoxy-benzyl)-3-oxo-butyric acid ethyl ester

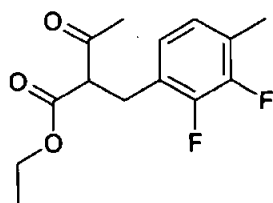


ESI-MS: $m/z = 321 [M-H]^-$

15

Example X

2-(2,3-Difluoro-4-methyl-benzyl)-3-oxo-butyric acid ethyl ester



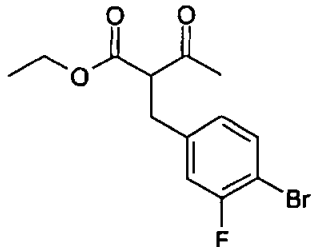
- To an ice-cold solution of 3-oxo-butyric acid ethyl ester (4.17 g, 32.1 mmol) and sodium iodide (23.9 g, 160 mmol) under Ar in acetonitrile (220 mL) was added over 3 min trimethylsilyl chloride (20.2 mL, 160 mmol) followed by 2,3-difluoro-4-methyl-benzaldehyde (5.0 g, 32.1 mmol). The ice bath was removed, and the reaction mixture was stirred at room temperature for 8 h and subsequently at 60 °C for 15 h. After cooling to room temperature the reaction mixture was poured into a mixture of EtOAc (300 mL) and water (200 mL). The organic phase was separated and washed with aqueous Na₂S₂O₃ solution and brine and dried over Na₂SO₄. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography (hexane/EtOAc 1:6) to give the product as a colorless oil.

Yield: 8.4 g (97%)

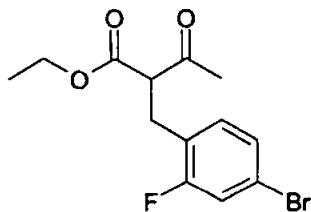
R_f 0.35 (silica gel, hexane/EtOAc 5:1)

- 15 The following compounds can be obtained in an analogous manner:

(1) 2-(4-Bromo-3-fluoro-benzyl)-3-oxo-butyric acid ethyl ester

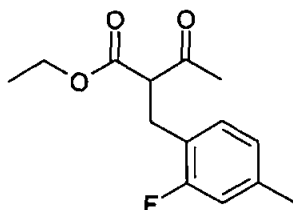
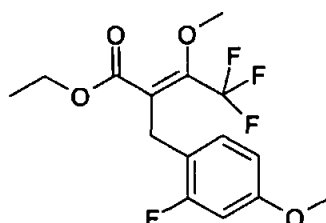


- 20 (2) 2-(4-Bromo-2-fluoro-benzyl)-3-oxo-butyric acid ethyl ester



R_f 0.42 (silica gel, hexane/EtOAc 4:1)

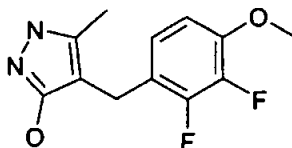
(3) 2-(2-fluoro-4-methyl-benzyl)-3-oxo-butyric acid ethyl ester

Example XI5 4,4,4-Trifluoro-2-(2-fluoro-4-methoxy-benzyl)-3-methoxy-but-2-enoic acid ethyl ester

To a 20 °C mixture of 4,4,4-trifluoro-2-(2-fluoro-4-methoxy-benzyl)-3-oxo-butyric acid ethyl ester (6.35 g, 19.7 mmol) and cesium carbonate (9.5 g, 28.9 mmol) in DMF (50 mL) was dropped a solution of toluene-4-sulfonic acid methyl ester (4.5 g, 23.7 mmol) in DMF (20 mL). The reaction mixture was stirred at room temperature over night and subsequently at 60 °C for 1.5 h. After cooling to room temperature diluted phosphoric acid was added, and the resultant solution was extracted with Et₂O. The combined organic phases were washed with brine and dried over Na₂SO₄. After removal of the solvent the residue was purified by chromatography on aluminum oxide (cyclohexane/EtOAc 99:1->70:30).

15 Yield: 6.6 g (100%)

ESI-MS: m/z = 337 [M+H]⁺

Example XII20 4-(2,3-Difluoro-4-methoxy-benzyl)-5-methyl-1H-pyrazol-3-ol

A solution of 2-(2,3-difluoro-4-methoxy-benzyl)-3-oxo-butyric acid ethyl ester (33.0 g, 0.115 mol) and hydrazine hydrate (80%, 8.0 g, 128 mmol) in EtOH (300 mL) was stirred at reflux

for 2 h. After cooling in an ice-bath the precipitate was collected, washed with cold EtOH, and dried *in vacuo* to give the product as a white solid.

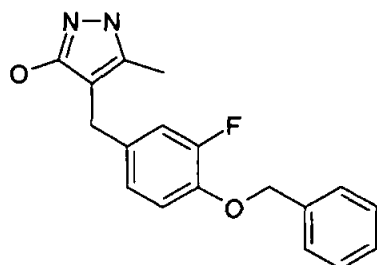
Yield: 22.5 g (70%)

ESI-MS: $m/z = 255$ $[M+H]^+$

5

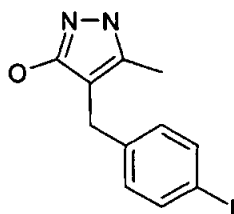
The following compounds can be obtained accordingly:

(1) 4-(4-Benzyloxy-3-fluoro-benzyl)-5-methyl-1H-pyrazol-3-ol



10 ESI-MS: $m/z = 313$ $[M+H]^+$

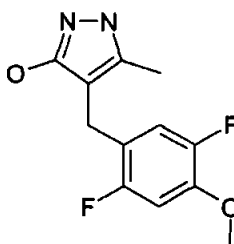
(2) 4-(4-Iodo-benzyl)-5-methyl-1H-pyrazol-3-ol



ESI-MS: $m/z = 315$ $[M+H]^+$

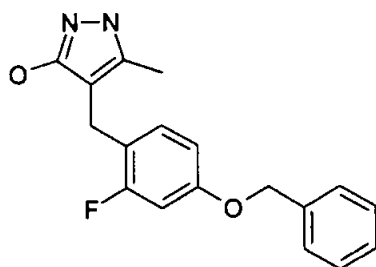
15

(3) 4-(2,5-Difluoro-4-methoxy-benzyl)-5-methyl-1H-pyrazol-3-ol



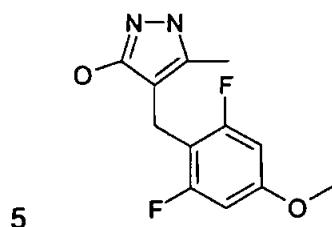
ESI-MS: $m/z = 255$ $[M+H]^+$

20 (4) 4-(4-Benzyloxy-2-fluoro-benzyl)-5-methyl-1H-pyrazol-3-ol



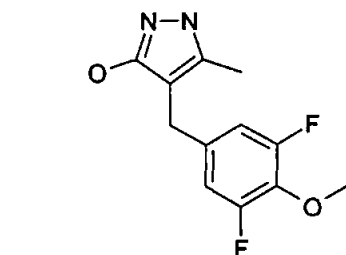
ESI-MS: $m/z = 313$ $[M+H]^+$

(5) 4-(2,6-Difluoro-4-methoxy-benzyl)-5-methyl-1H-pyrazol-3-ol



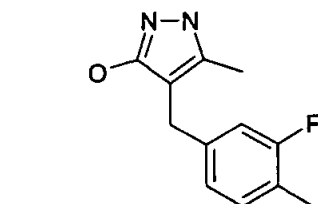
ESI-MS: $m/z = 255$ $[M+H]^+$

(6) 4-(3,5-Difluoro-4-methoxy-benzyl)-5-methyl-1H-pyrazol-3-ol



ESI-MS: $m/z = 255$ $[M+H]^+$

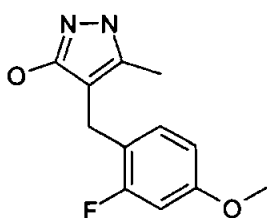
(7) 4-(3-Fluoro-4-methyl-benzyl)-5-methyl-1H-pyrazol-3-ol



ESI-MS: $m/z = 221$ $[M+H]^+$

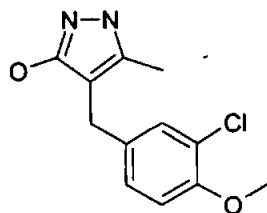
(8) 4-(2-Fluoro-4-methoxy-benzyl)-5-methyl-1H-pyrazol-3-ol

57



ESI-MS: $m/z = 237 [M+H]^+$

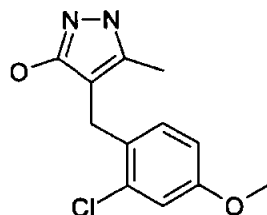
(9) 4-(3-Chloro-4-methoxy-benzyl)-5-methyl-1H-pyrazol-3-ol



5

ESI-MS: $m/z = 253/255 [M+H]^+$ (chlorine)

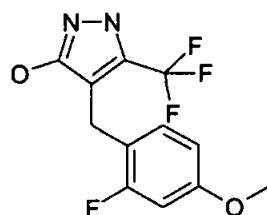
(10) 4-(2-Chloro-4-methoxy-benzyl)-5-methyl-1H-pyrazol-3-ol



10

ESI-MS: $m/z = 253/255 [M+H]^+$ (chlorine)

(11) 4-(2-Fluoro-4-methoxy-benzyl)-5-trifluoromethyl-1H-pyrazol-3-ol

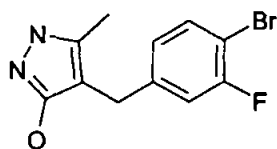


15

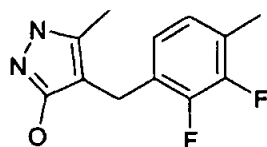
The product was prepared following the procedure above starting from 4,4,4-trifluoro-2-(2-fluoro-4-methoxy-benzyl)-3-methoxy-but-2-enoic acid ethyl ester

ESI-MS: $m/z = 289 [M-H]^-$

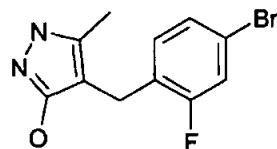
(12) 4-(4-Bromo-3-fluoro-benzyl)-5-methyl-1H-pyrazol-3-ol



(13) 4-(2,3-Difluoro-4-methyl-benzyl)-5-methyl-1H-pyrazol-3-ol

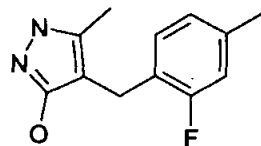
5 R_f 0.05 (silica gel, hexane/EtOAc 5:1)

(14) 4-(4-Bromo-2-fluoro-benzyl)-5-methyl-1H-pyrazol-3-ol

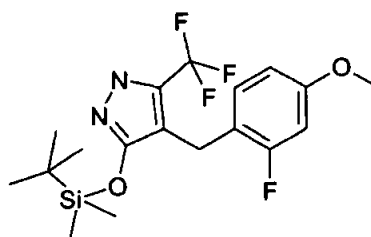
R_f 0.15 (silica gel, hexane/EtOAc 1:1)

10

(15) 4-(2-Fluoro-4-methyl-benzyl)-5-methyl-1H-pyrazol-3-ol

R_f 0.11 (silica gel, hexane/EtOAc 1:1)

15

Example XIII3-(tert-Butyl-dimethyl-silyloxy)-4-(2-fluoro-4-methoxy-benzyl)-5-trifluoromethyl-1H-pyrazole

To a solution of 4-(2-fluoro-4-methoxy-benzyl)-5-trifluoromethyl-1H-pyrazol-3-ol (0.21 g, 0.72 mmol) and imidazole (8.0 g, 128 mmol) in DMF (2 mL) was added tert-

20

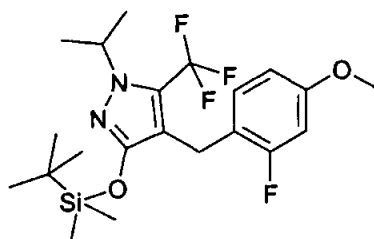
butyldimethylsilylchloride (0.13 g, 0.86 mmol). After stirring at room temperature for 4 h, the solution was diluted with EtOAc and washed with water and brine. The organic phase was dried and the solvent removed.

Yield: 0.34 g (ca. 80% pure)

5 ESI-MS: $m/z = 405 [M+H]^+$

Example XIV

3-(tert-Butyl-dimethyl-silyloxy)-4-(2-fluoro-4-methoxy-benzyl)-1-isopropyl-5-trifluoromethyl-1H-pyrazole



10

To a suspension of 3-(tert-butyl-dimethyl-silyloxy)-4-(2-fluoro-4-methoxy-benzyl)-5-trifluoromethyl-1H-pyrazole (0.27 g, 0.67 mmol) and Ph_3P (0.20 g, 0.76 mmol) in isopropanol (2 mL) was added diethyl azodicarboxylate in toluene (40%, 0.35 mL, 0.76 mmol). The solution was stirred at room temperature for 1 h and then diluted with Et_2O . The resultant solution was washed with water and aqueous NaOH solution (2 N), dried over Na_2SO_4 , and the solvent was removed. The residue was purified by chromatography on silica gel (cyclohexane/EtOAc 99:1-4:1) to give the product as a colorless oil.

15

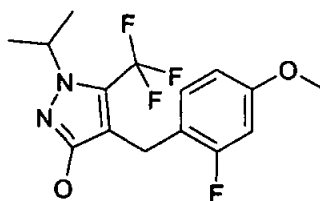
Yield: 0.14 g (47%)

ESI-MS: $m/z = 447 [M+H]^+$

20

Example XV

4-(2-Fluoro-4-methoxy-benzyl)-1-isopropyl-5-trifluoromethyl-1H-pyrazol-3-ol



A solution of 3-(tert-butyl-dimethyl-silyloxy)-4-(2-fluoro-4-methoxy-benzyl)-1-isopropyl-5-trifluoromethyl-1H-pyrazole (0.27 g, 0.67 mmol), aqueous HCl (1 N, 1 mL, 1 mmol), MeOH (0.5 mL), and THF (12 mL) was stirred at 60 °C for 2 h. After cooling to room temperature

25

the solution was diluted with EtOAc and washed with water and brine. The product was yielded as a white solid after drying over Na₂SO₄ and removal of the solvent *in vacuo*.

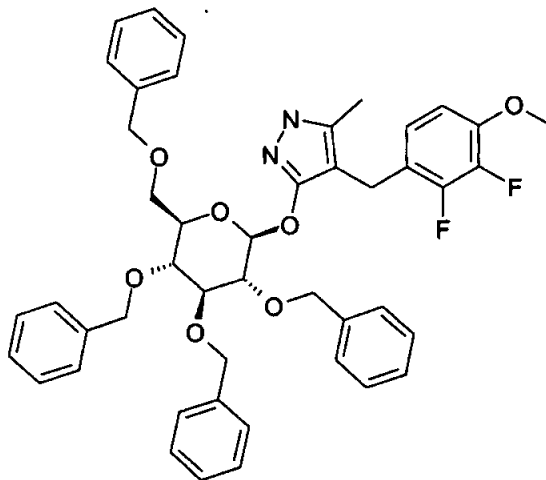
Yield: 0.10 g (100%)

ESI-MS: $m/z = 333 [M+H]^+$

5

Example XVI

4-(2,3-Difluoro-4-methoxy-benzyl)-5-methyl-3-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



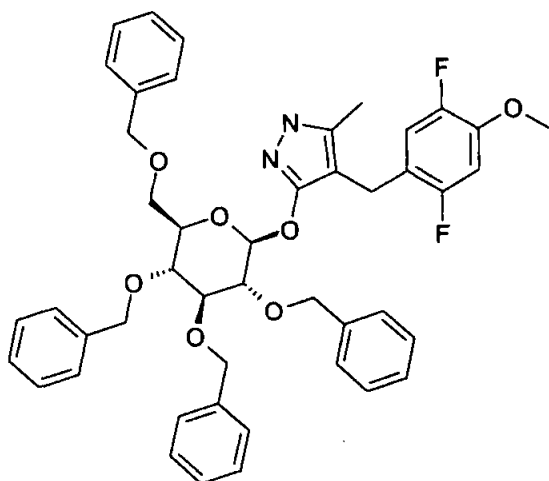
- 10 To a 0 °C solution of 4-(2,3-Difluoro-4-methoxy-benzyl)-5-methyl-1H-pyrazol-3-ol (2.14 g, 8.4 mmol), 2,3,4,6-tetra-O-benzyl-α-D-glucopyranose (4.54 g, 8.4 mmol), and PPh₃ (2.20 g, 8.4 mmol) in dry THF (80 mL) was added diethyl azodicarboxylate in toluene (40%, 3.85 mL, 8.4 mmol) at a rate such that the solution maintained 2-6 °C. After 10 min the cooling bath was removed, and the reaction solution was stirred at room temperature over night. Then the
- 15 solution was concentrated at 40 °C under reduced pressure, and the remainder was treated with Et₂O (50 mL). The ether solution was cooled to -18 °C, and the forming precipitate was separated and washed with cold Et₂O. The filtrate was diluted with Et₂O and washed with aqueous NaOH solution (2 N), water, and brine. After drying over MgSO₄ and evaporation of the solvent, the residue was purified by chromatography on silica gel (cyclohexane/EtOAc
- 20 2:1->1:6). The purified product was recrystallized from iPr₂O to give the product as a white solid (<5% α anomer).

Yield: 3.10 g (48%)

ESI-MS: $m/z = 777 [M+H]^+$

- 25 The following compounds can be obtained accordingly:

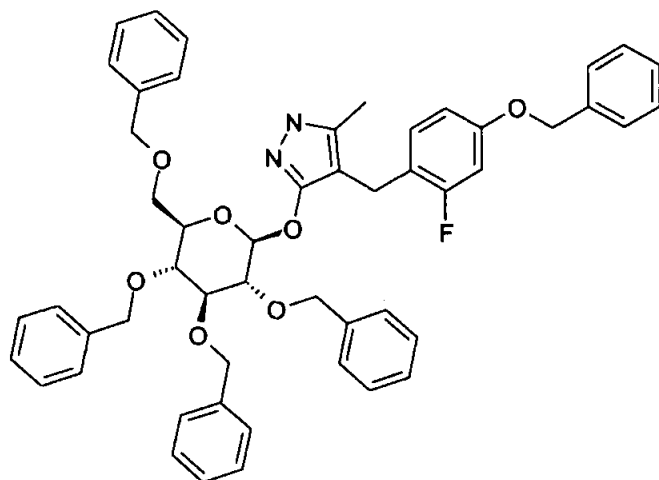
(1) 4-(2,5-Difluoro-4-methoxy-benzyl)-5-methyl-3-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



ESI-MS: $m/z = 777 [M+H]^+$

5

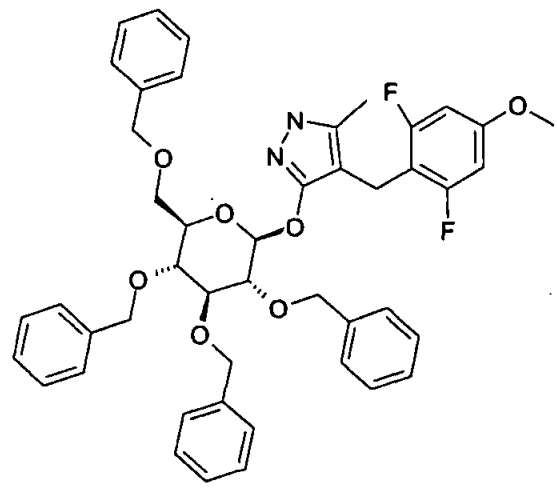
(2) 4-(2-Fluoro-4-benzyloxy-benzyl)-5-methyl-3-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



ESI-MS: $m/z = 835 [M+H]^+$

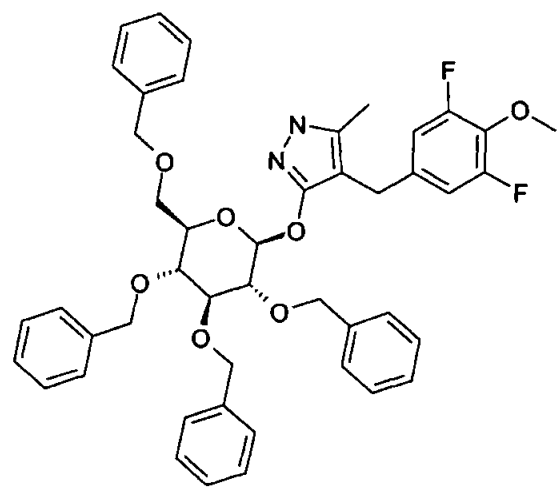
10

(3) 4-(2,6-Difluoro-4-methoxy-benzyl)-5-methyl-3-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



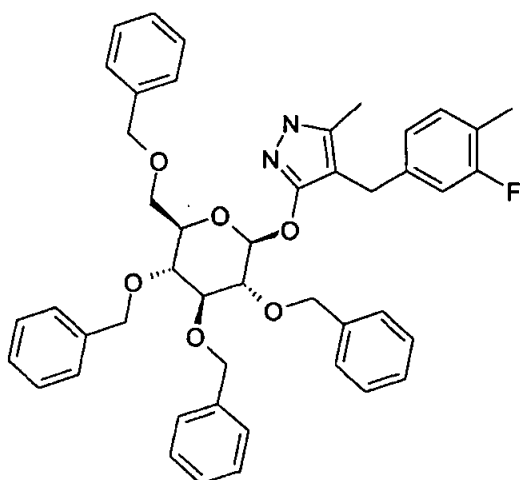
ESI-MS: $m/z = 777 [M+H]^+$

5 (4) 4-(3,5-Difluoro-4-methoxy-benzyl)-5-methyl-3-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



ESI-MS: $m/z = 777 [M+H]^+$

10 (5) 4-(3-Fluoro-4-methyl-benzyl)-5-methyl-3-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole

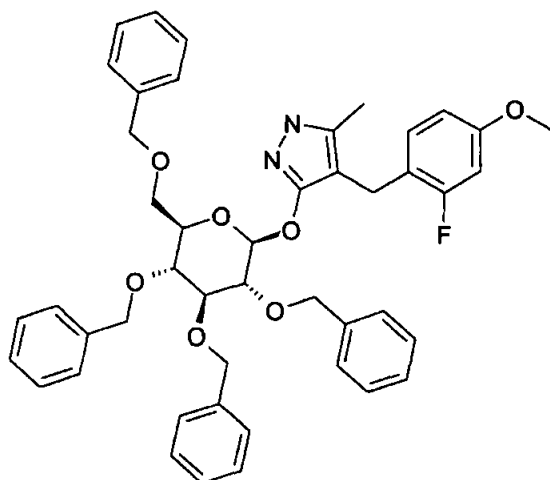


Bu₃P and 1,1'-(azodicarbonyl)-dipiperidine were used instead of Ph₃P and diethyl azodicarboxylate

ESI-MS: $m/z = 743 [M+H]^+$

5

(6) 4-(2-Fluoro-4-methoxy-benzyl)-5-methyl-3-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole

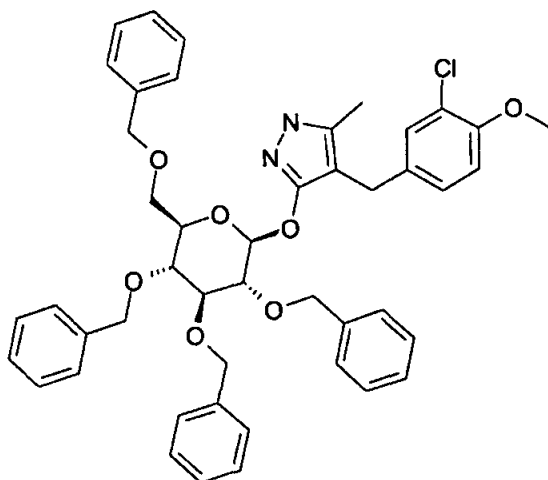


Bu₃P and 1,1'-(azodicarbonyl)-dipiperidine were used instead of Ph₃P and diethyl azodicarboxylate

10

ESI-MS: $m/z = 759 [M+H]^+$

(7) 4-(3-Chloro-4-methoxy-benzyl)-5-methyl-3-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole

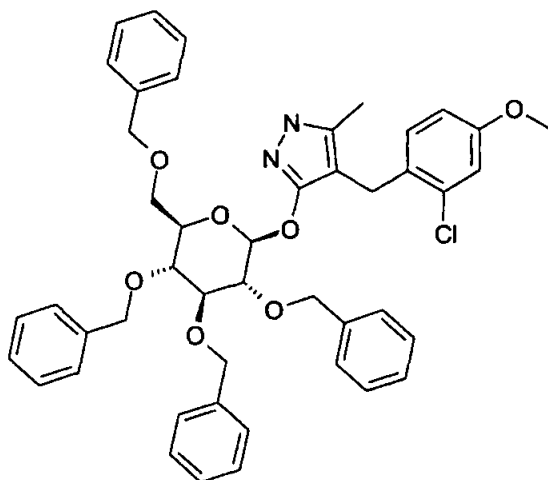


Bu₃P and 1,1'-(azodicarbonyl)-dipiperidine were used instead of Ph₃P and diethyl azodicarboxylate

ESI-MS: m/z = 775/777 [M+H]⁺ (chlorine)

5

(8) 4-(2-Chloro-4-methoxy-benzyl)-5-methyl-3-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole

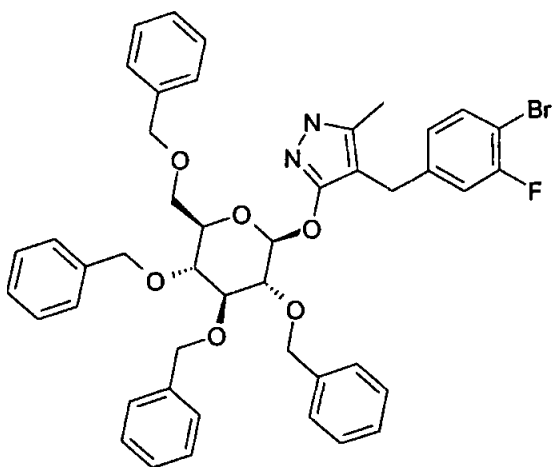


Bu₃P and 1,1'-(azodicarbonyl)-dipiperidine were used instead of Ph₃P and diethyl azodicarboxylate

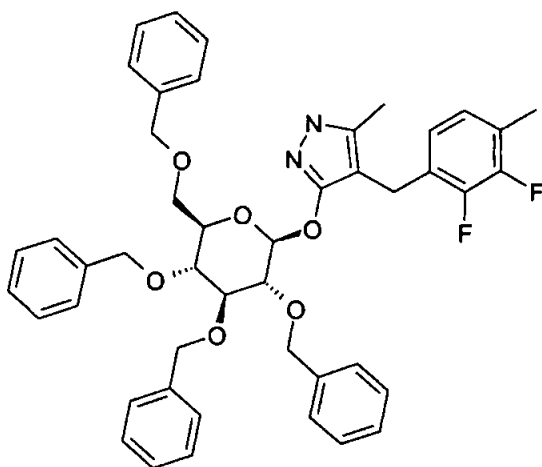
10

ESI-MS: m/z = 775/777 [M+H]⁺ (chlorine)

(9) 4-(4-Bromo-3-fluoro-benzyl)-5-methyl-3-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



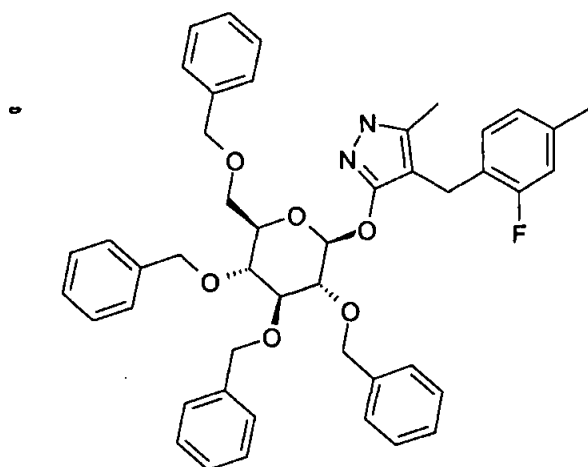
(10) 4-(2,3-Difluoro-4-methyl-benzyl)-5-methyl-3-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



5

R_f 0.24 (silica gel, hexane/EtOAc 1:1)

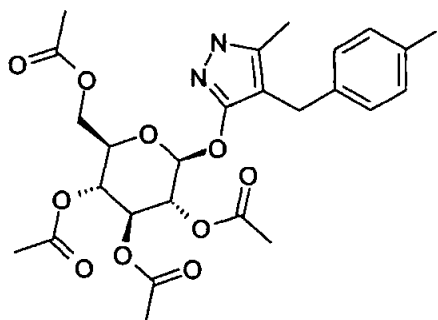
(11) 4-(2-Fluoro-4-methyl-benzyl)-5-methyl-3-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



R_f 0.48 (silica gel, hexane/EtOAc 1:1)

Example XVII

5 4-(4-iodo-benzyl)-5-methyl-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



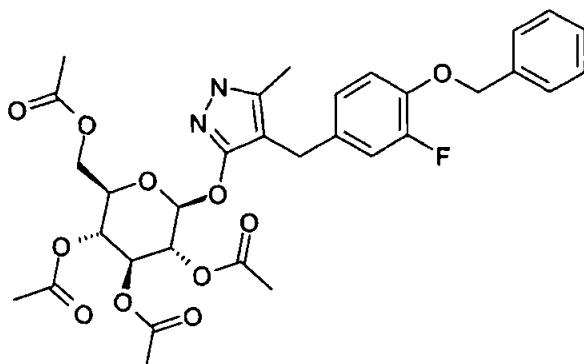
To a solution of 4-(4-iodo-benzyl)-5-methyl-1H-pyrazol-3-ol (0.70 g, 2.23 mmol) in dry THF (80 mL) was added Ag₂CO₃ (0.65 g, 2.36 mmol) followed by 2,3,4,6-tetra-O-acetyl-β-D-glucopyranos-1-ylbromide (1.00 g, 2.43 mmol). The reaction mixture was stirred at reflux in the dark over night prior to the addition of another portion of Ag₂CO₃ (0.75 g, 2.72 mmol) and 2,3,4,6-tetra-O-acetyl-β-D-glucopyranos-1-ylbromide (1.10 g, 2.68 mmol). The reaction mixture was stirred at reflux for another night and then cooled to room temperature. The mixture was filtrated, and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography on silica gel (CH₂Cl₂/MeOH 1:0->10:1) to give the product as a white solid.

15 Yield: 0.40 g (28%)

ESI-MS: m/z = 645 [M+H]⁺

The following compounds can be obtained accordingly:

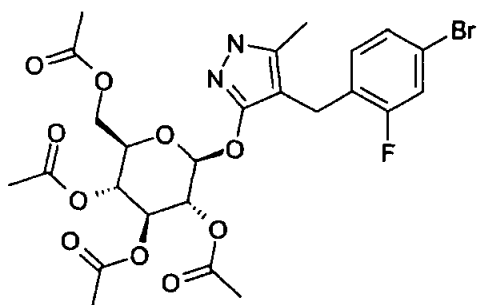
(1) 4-(4-benzyloxy-3-fluoro-benzyl)-5-methyl-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



ESI-MS: $m/z = 643 [M+H]^+$

5

(2) 4-(4-Bromo-2-fluoro-benzyl)-5-methyl-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole

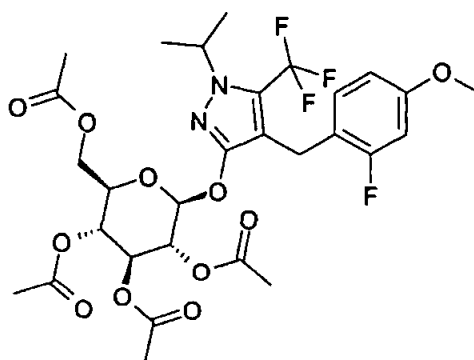


R_f 0.46 (silica gel, hexane/EtOAc 1:1)

10

Example XVIII

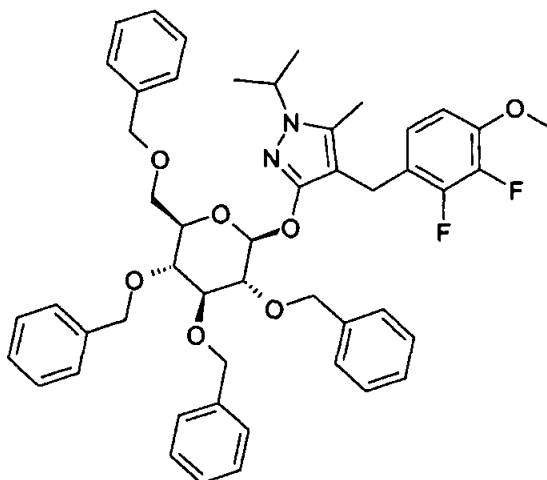
4-(2-fluoro-4-methoxy-benzyl)-5-trifluoromethyl-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



- To a solution of 4-(2-Fluoro-4-methoxy-benzyl)-1-isopropyl-5-trifluoromethyl-1H-pyrazol-3-ol (1.84 g, 5.54 mmol), K_2CO_3 (7.5 g, 54.3 mmol), and nBu_3BnNCl (0.25 g, 0.8 mmol) in water (5 mL) and CH_2Cl_2 (25 mL) was added 2,3,4,6-tetra-O-acetyl- β -D-glucopyranos-1-ylbromide (3.80 g, 8.78 mmol). The reaction mixture was stirred vigorously at room temperature in the dark over night. Then CH_2Cl_2 was added and the organic layer was separated. After washing with water and 1 M phosphoric acid, the organic phase was dried over Na_2SO_4 , and the solvent was removed. The residue was purified by chromatography on silica gel (cyclohexane/EtOAc 3:2->0:1).
- Yield: 2.42 g (ca. 50% pure)
- ESI-MS: $m/z = 663 [M+H]^+$

Example XIX

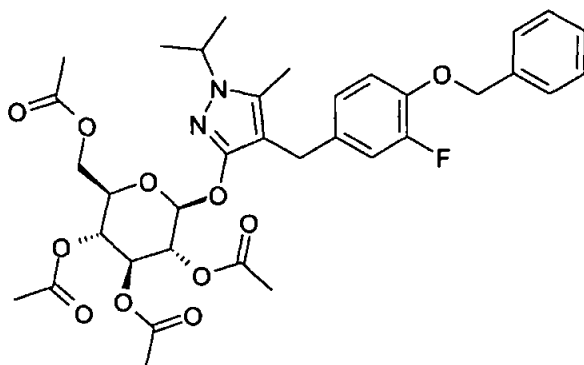
4-(2,3-Difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(2,3,4,6-tetra-O-benzyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole



- To a 20 °C mixture of 4-(2,3-difluoro-4-methoxy-benzyl)-5-methyl-3-(2,3,4,6-tetra-O-benzyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole (2.90 g, 3.7 mmol) and Cs_2CO_3 (12.30 g, 37.8 mmol) in DMF (56 mL) was added isopropyl iodide (1.90 mL, 18.9 mmol). The reaction mixture was stirred at room temperature for 2.5 h. Then the reaction mixture was poured into water (300 mL), and the resultant solution was extracted with EtOAc. The combined organic extracts were washed with water and brine and dried over $MgSO_4$. The organic solution was concentrated at 40 °C under reduced pressure, and the residue was purified by chromatography on silica gel (cyclohexane/EtOAc 6:1->1:1).
- Yield: 2.10 g (69%)
- ESI-MS: $m/z = 459 [M+H]^+$

The following compounds can be obtained accordingly:

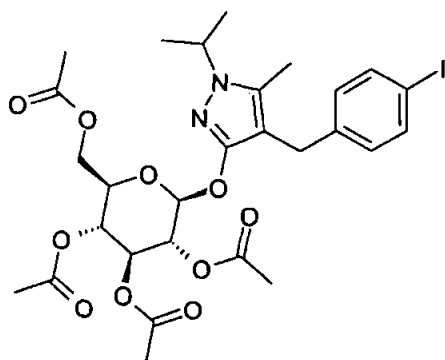
(1) 4-(4-benzyloxy-3-fluoro-benzyl)-1-isopropyl-5-methyl-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



5

ESI-MS: $m/z = 685 [M+H]^+$

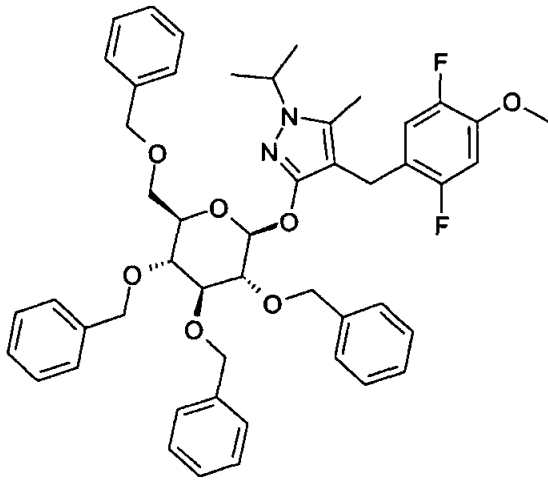
(2) 4-(4-iodo-benzyl)-1-isopropyl-5-methyl-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



10

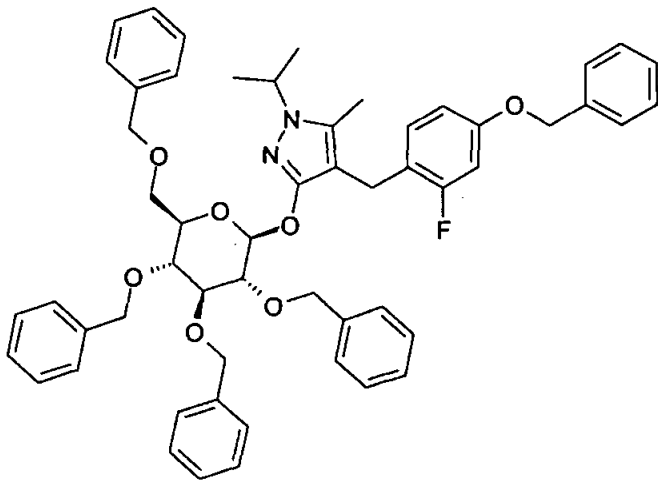
ESI-MS: $m/z = 687 [M+H]^+$

(3) 4-(2,5-Difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



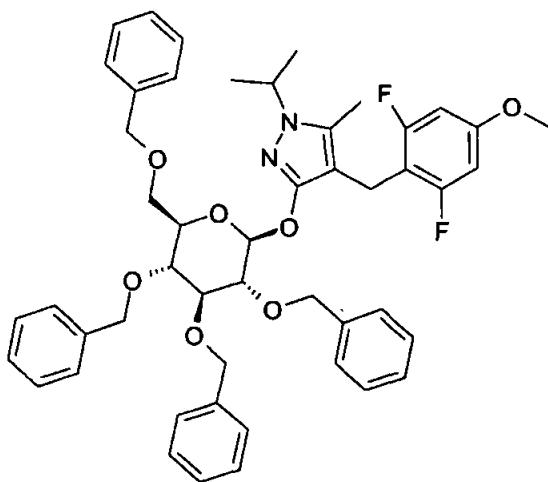
ESI-MS: $m/z = 819 [M+H]^+$

5 (4) 4-(2-Fluoro-4-benzyloxy-benzyl)-1-isopropyl-5-methyl-3-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



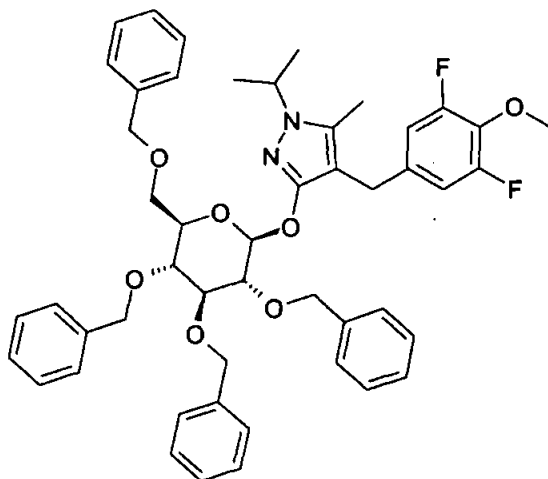
ESI-MS: $m/z = 877 [M+H]^+$

10 (5) 4-(2,6-Difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



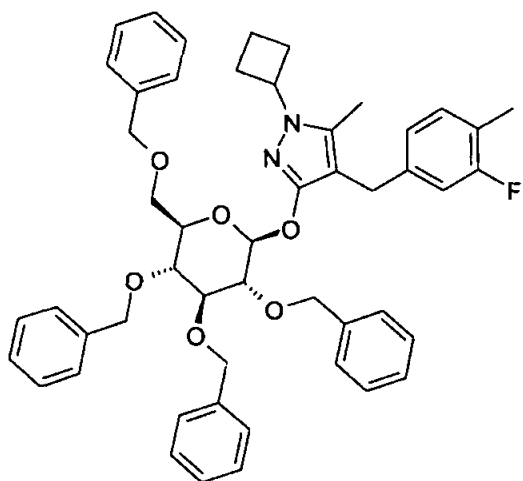
ESI-MS: $m/z = 819 [M+H]^+$

- 5 (6) 4-(3,5-Difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



ESI-MS: $m/z = 819 [M+H]^+$

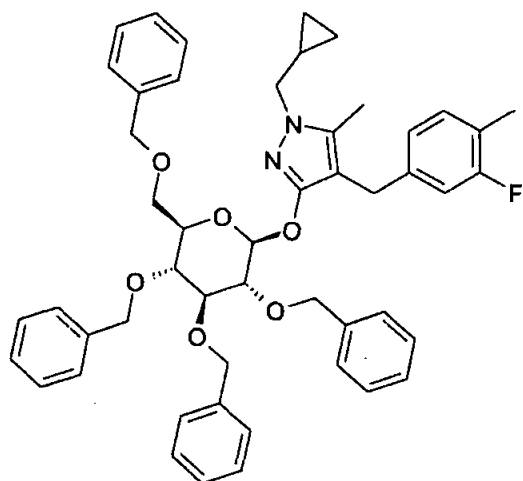
- 10 (7) 1-Cyclobutyl-4-(3-fluoro-4-methyl-benzyl)-5-methyl-3-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



Bromo-cyclobutane was used as the electrophile instead of isopropyl iodide

ESI-MS: $m/z = 797 [M+H]^+$

- 5 (8) 1-Cyclopropylmethyl-4-(3-fluoro-4-methyl-benzyl)-5-methyl-3-(2,3,4,6-tetra-O-benzyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole

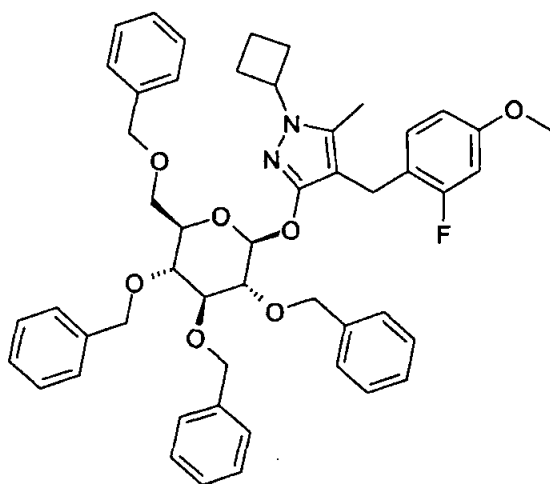


Yielded as a side product in the preparation of example XVIII(7)

ESI-MS: $m/z = 797 [M+H]^+$

10

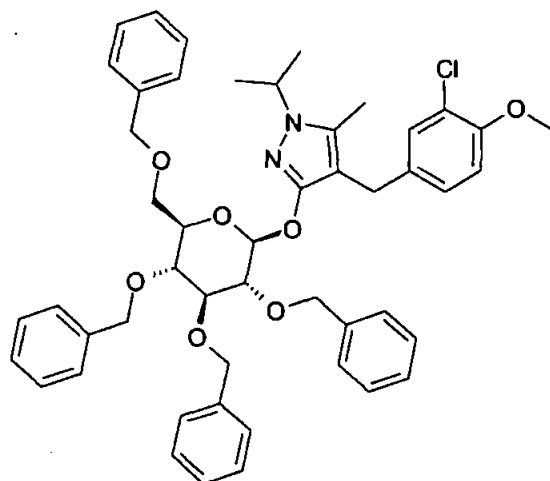
- (9) 1-Cyclobutyl-4-(2-fluoro-4-methoxy-benzyl)-5-methyl-3-(2,3,4,6-tetra-O-benzyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole



Bromo-cyclobutane was used as the electrophile instead of isopropyl iodide

ESI-MS: $m/z = 813 [M+H]^+$

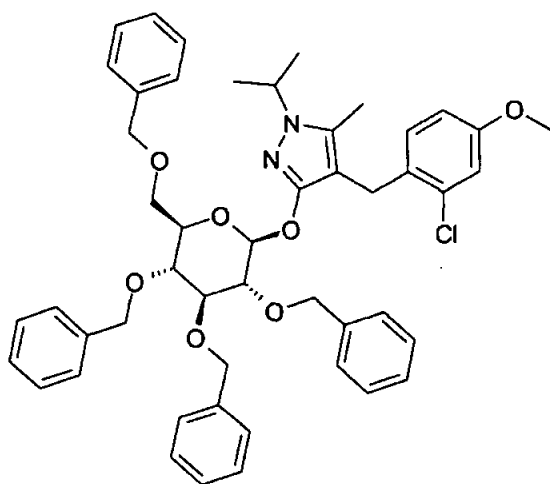
- 5 (10) 4-(3-Chloro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(2,3,4,6-tetra-O-benzyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole



The reaction is preferably carried out with potassium hexamethyldisilazide as the base in toluene and THF

- 10 ESI-MS: $m/z = 817/819 [M+H]^+$ (chlorine)

(11) 4-(2-Chloro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(2,3,4,6-tetra-O-benzyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole

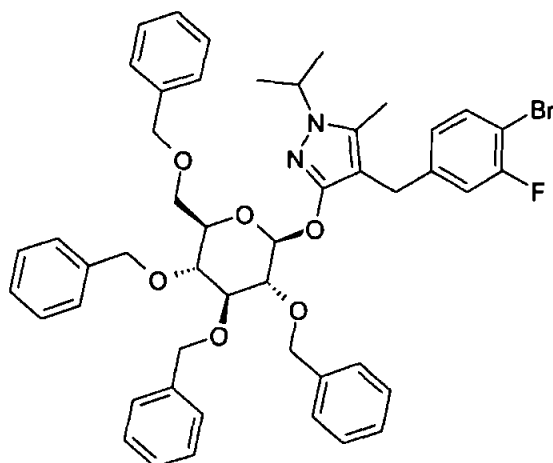


The reaction is preferably carried out with potassium hexamethyldisilazide as the base in toluene and THF

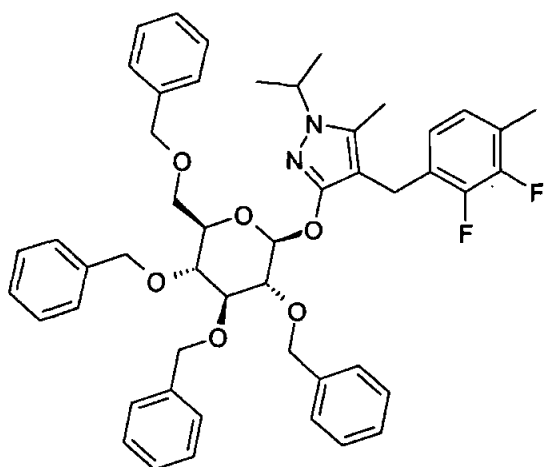
ESI-MS: $m/z = 817/819 [M+H]^+$ (chlorine)

5

(12) 4-(4-Bromo-3-fluoro-benzyl)-1-isopropyl-5-methyl-3-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole

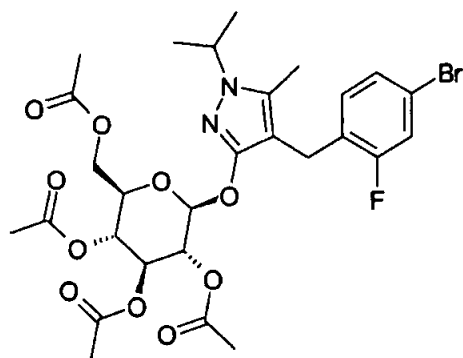


10 (13) 4-(2,3-Difluoro-4-methyl-benzyl)-1-isopropyl-5-methyl-3-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



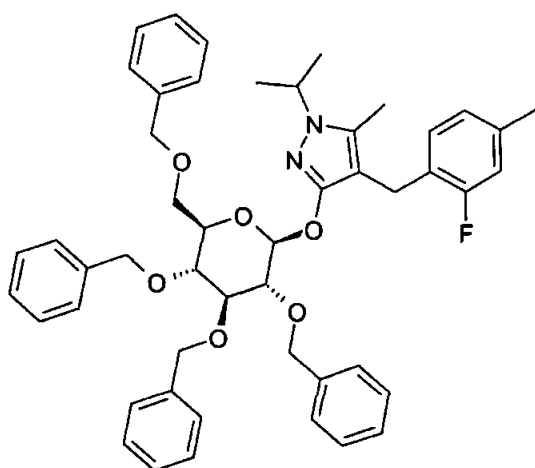
R_f 0.65 (silica gel, hexane/EtOAc 1:1)

- 5 (14) 4-(4-Bromo-2-fluoro-benzyl)-1-isopropyl-5-methyl-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



R_f 0.50 (silica gel, hexane/EtOAc 1:1)

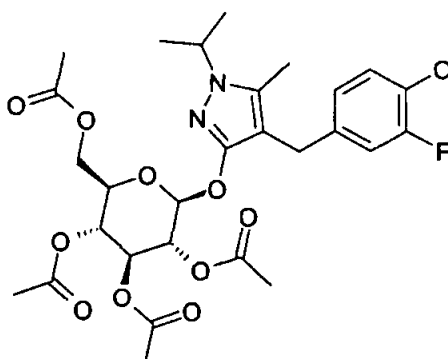
- 10 (15) 4-(2-Fluoro-4-methyl-benzyl)-1-isopropyl-5-methyl-3-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



R_f 0.53 (silica gel, hexane/EtOAc 4:1)

5 Example XX

4-(3-fluoro-4-hydroxy-benzyl)-1-isopropyl-5-methyl-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



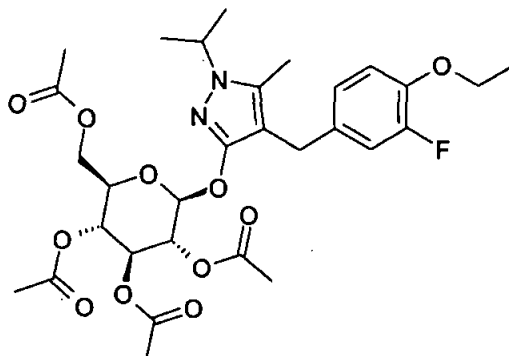
10 A mixture of 4-(4-benzyloxy-3-fluoro-benzyl)-1-isopropyl-5-methyl-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole (0.26 g, 0.38 mmol) and 10% Pd on carbon (0.05 g) in EtOAc (10 mL) was stirred at room temperature under hydrogen atmosphere (3 bar). After 3 h the catalyst was separated by filtration, and the solvent was removed under reduced pressure. The residue was dissolved in Et₂O, filtered over Celite®, and concentrated *in vacuo*.

15 Yield: 0.22 g (97%)

ESI-MS: m/z = 595 [M+H]⁺

Example XXI

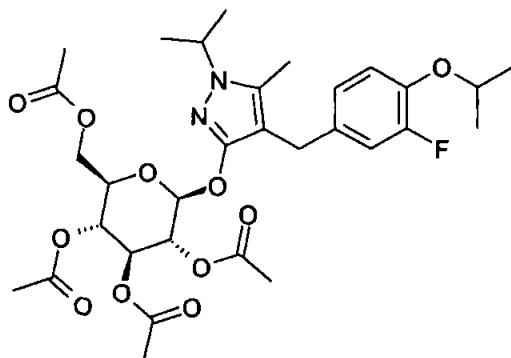
4-(3-Fluoro-4-ethoxy-benzyl)-1-isopropyl-5-methyl-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



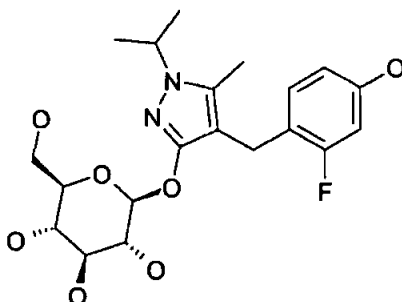
- 5 To a suspension of 4-(3-fluoro-4-hydroxy-benzyl)-1-isopropyl-5-methyl-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole (0.22 g, 0.37 mmol) and cesium carbonate (0.31 g, 0.40 mmol) in DMF (3 mL) was added ethyl bromide (30 μL, 0.40 mmol). After stirring at ambient temperature for 5 h, the mixture was poured into a mixture of EtOAc and phosphoric acid (0.1 M). The organic phase was separated, washed with aqueous NaHCO₃
- 10 solution and brine, and dried over Na₂SO₄. The organic solution was concentrated, and the residue was purified by silica gel chromatography (petrol ether/EtOAc 1:1).
Yield: 0.18 g (78%)
ESI-MS: m/z = 623 [M+H]⁺

- 15 The following compound can be obtained accordingly:

(1) 4-(3-Fluoro-4-isopropoxy-benzyl)-1-isopropyl-5-methyl-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



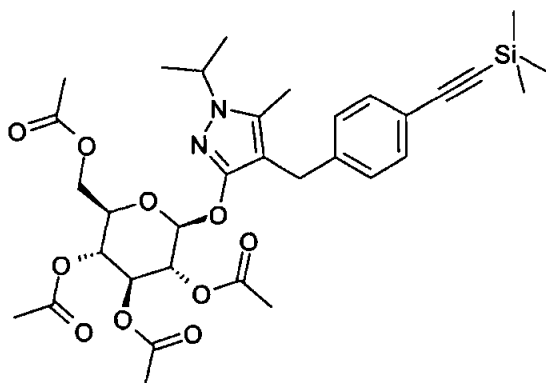
- 20 ESI-MS: m/z = 637 [M+H]⁺

Example XXII4-(2-fluoro-4-hydroxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole

A mixture of 4-(2-fluoro-4-benzyloxy-benzyl)-1-isopropyl-5-methyl-3-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole (2.0 g, 2.3 mmol) and 20% Pd on carbon (1.0 g) in EtOH (70 mL) was stirred at room temperature under hydrogen atmosphere (50 psi). After 2 h the catalyst was separated by filtration, and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (CH₂Cl₂/MeOH 10:1→3:1).

Yield: 0.69 g (71%)

ESI-MS: $m/z = 427 [M+H]^+$

Example XXIII4-(4-Trimethylsilyl-ethynyl-benzyl)-1-isopropyl-5-methyl-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole

15

To a degassed solution of 4-(4-iodo-benzyl)-1-isopropyl-5-methyl-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole (0.31 g, 0.45 mmol) in DMF (5 mL) under Ar was added in the given order NEt₃ (0.2 mL, 1.43 mmol), CuI (0.02 g, 0.11 mmol), (Ph₃P)₂PdCl₂ (0.05 g, 0.07 mmol), and trimethylsilylacetylen (0.10 mL, 0.69 mmol). The reaction mixture was stirred at 90 °C for 3.5 h. After cooling to room temperature EtOAc was added, and the resultant solution was washed with aqueous NaHCO₃ solution and dried over Na₂SO₄. The

20

solvent was evaporated, and the residue was purified by chromatography on silica gel (cyclohexane/EtOAc 9:1→1:1) to give the product as a yellow oil.

Yield: 0.18 g (64%)

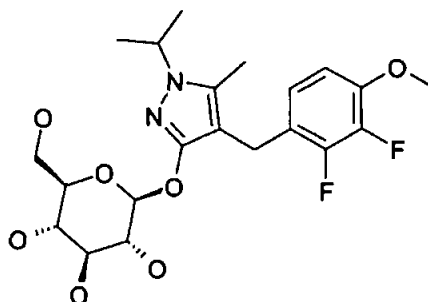
ESI-MS: $m/z = 657 [M+H]^+$

5

Preparation of Products

Example 1

10 (1) 4-(2,3-Difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole



15 A mixture of 4-(2,3-difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole (1.80 g, 2.2 mmol) and 20% Pd on carbon (1 g) in EtOH (50 mL) was stirred at room temperature under hydrogen atmosphere (50 psi). After 2.5 h the catalyst was separated by filtration, and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (DCM/MeOH 1:0→4:1) to afford the product as a white solid.

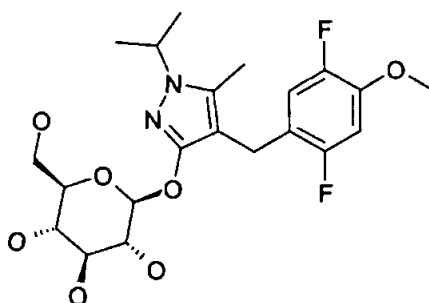
Yield: 0.48 g (48%)

ESI-MS: $m/z = 459 [M+H]^+$

20

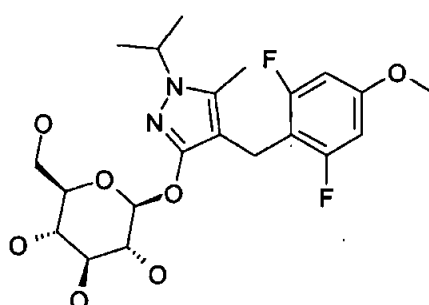
The following compounds can be obtained accordingly:

(2) 4-(2,5-Difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole



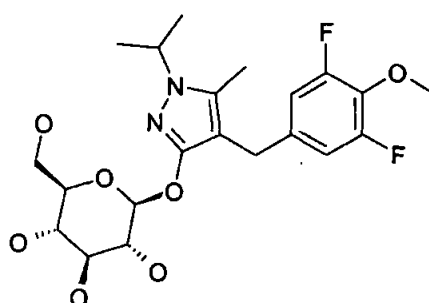
ESI-MS: $m/z = 459 [M+H]^+$

- 5 (3) 4-(2,6-Difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole



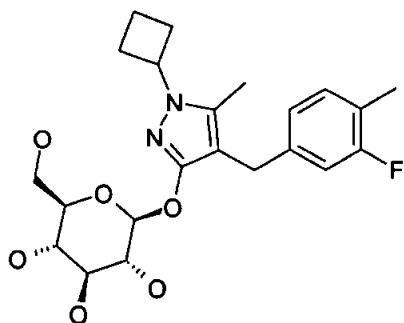
ESI-MS: $m/z = 459 [M+H]^+$

- 10 (4) 4-(3,5-Difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole



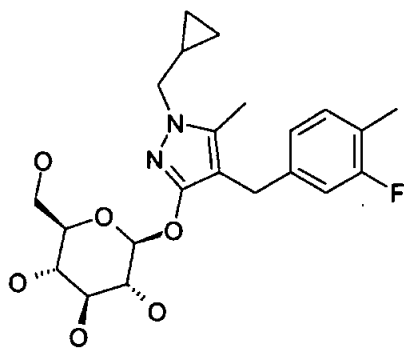
ESI-MS: $m/z = 459 [M+H]^+$

- 15 (5) 1-Cyclobutyl-4-(3-fluoro-4-methyl-benzyl)-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole



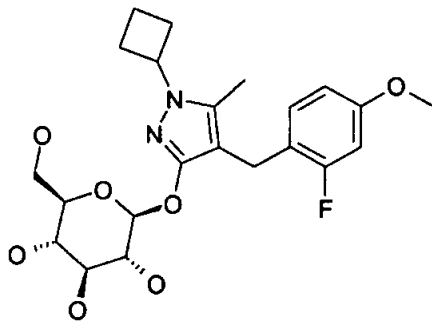
ESI-MS: $m/z = 437 [M+H]^+$

5 (6) 1-Cyclopropylmethyl-4-(3-fluoro-4-methyl-benzyl)-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole



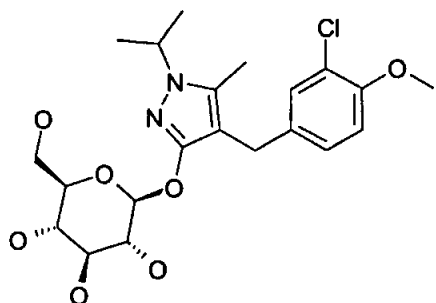
ESI-MS: $m/z = 437 [M+H]^+$

10 (7) 1-Cyclobutyl-4-(2-fluoro-4-methoxy-benzyl)-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole



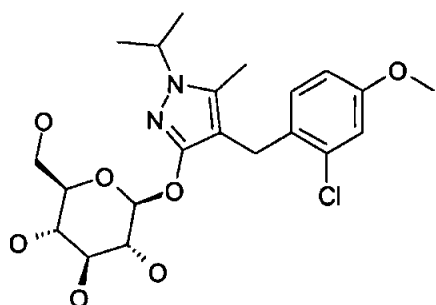
ESI-MS: $m/z = 453 [M+H]^+$

15 (8) 4-(3-Chloro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole



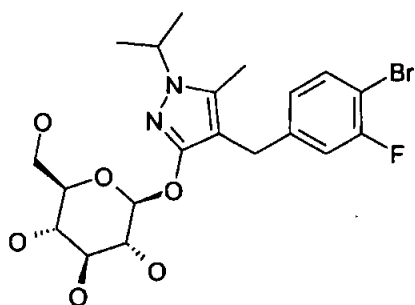
ESI-MS: $m/z = 457/459$ $[M+H]^+$ (chlorine)

- 5 (9) 4-(2-Chloro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole

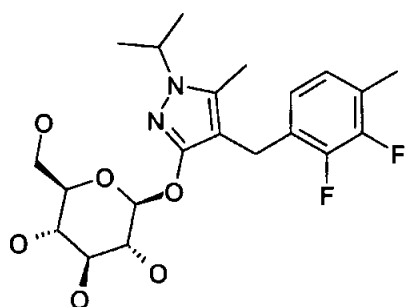


ESI-MS: $m/z = 457/459$ $[M+H]^+$ (chlorine)

- 10 (10) 4-(4-Bromo-3-fluoro-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole

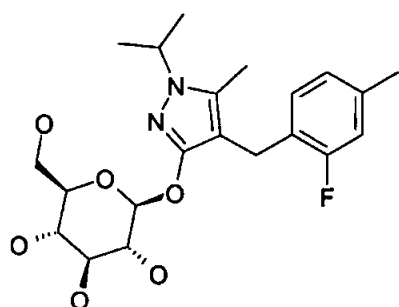


- (11) 4-(2,3-Difluoro-4-methyl-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole



R_f 0.24 (silica gel, CHCl₃/MeOH 9:1)

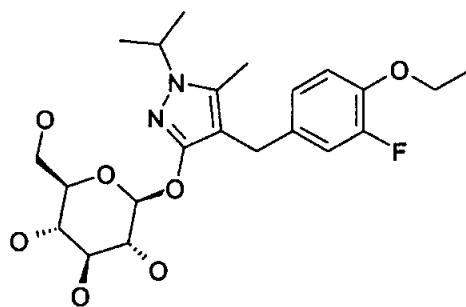
- 5 (12) 4-(2-Fluoro-4-methyl-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole



R_f 0.24 (silica gel, CH₂Cl₂/MeOH 9:1)

10 Example 2

- (13) 4-(3-Fluoro-4-ethoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole



- 15 To an ice-cold solution of 4-(4-ethoxy-3-fluoro-benzyl)-1-isopropyl-5-methyl-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole (0.17 g, 0.27 mmol) in MeOH (1 mL) and THF (1.5 mL) was added aqueous LiOH solution (1 M, 1.25 mL). The solution was stirred in the ice-bath for 1 h and then diluted with EtOAc and water. The organic phase was

separated, washed with water and brine, and dried over Na₂SO₄. The solvent was removed, and the residue was dried *in vacuo* to give the product as a white foam.

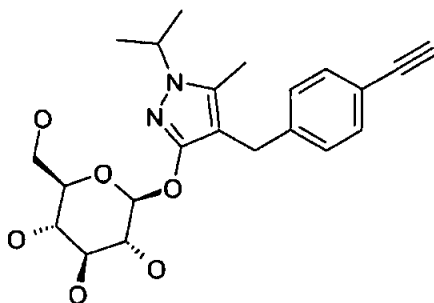
Yield: 0.12 g (95%)

ESI-MS: $m/z = 455$ [M+H]⁺

5

The following compounds can be obtained accordingly:

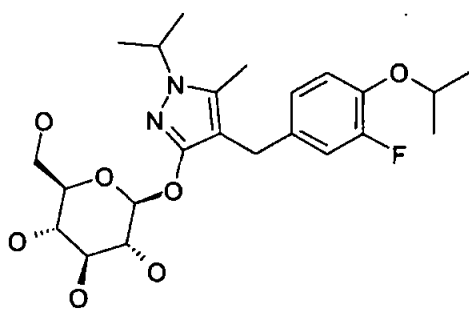
(14) 4-(4-ethynyl-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole



- 10 4-(4-Trimethylsilyl-ethynyl-benzyl)-1-isopropyl-5-methyl-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole was subjected to the reaction conditions described above.

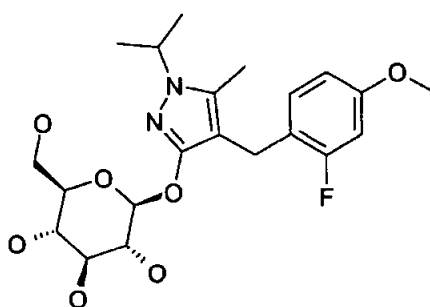
ESI-MS: $m/z = 417$ [M+H]⁺

- 15 (15) 4-(3-Fluoro-4-isopropoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole

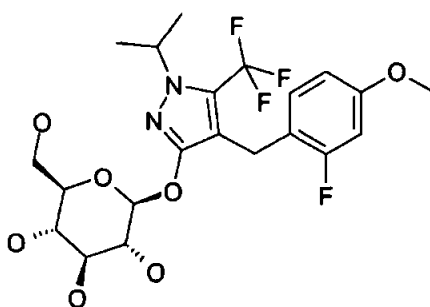


ESI-MS: $m/z = 469$ [M+H]⁺

- 20 (16) 4-(2-fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole



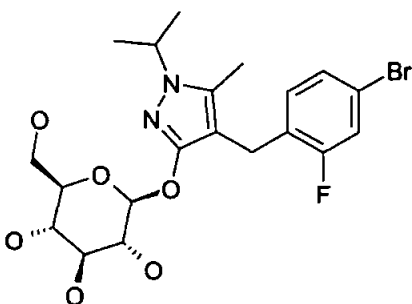
(17) 4-(2-fluoro-4-methoxy-benzyl)-1-isopropyl-5-trifluoromethyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole



5

ESI-MS: $m/z = 495 [M+H]^+$

(18) 4-(4-Bromo-2-fluoro-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole

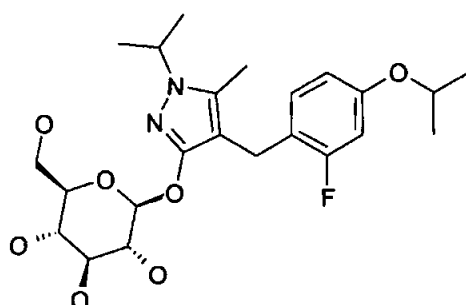


10

R_f 0.29 (silica gel, $CH_2Cl_2/MeOH$ 9:1)

Example 3

15 (19) 4-(2-Fluoro-4-isopropoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole



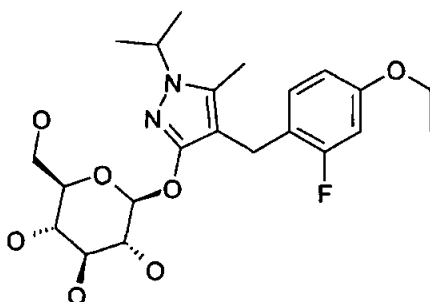
To a suspension of 4-(2-fluoro-4-hydroxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole (0.20 g, 0.47 mmol) and cesium carbonate (0.16 g, 0.50 mmol) in DMF (3.5 mL) was added isopropyl iodide (52 μL, 0.50 mmol). After stirring the mixture at ambient temperature over night, another portion of cesium carbonate (0.10 g) and isopropyl iodide (30 μL) were added. After stirring another 24 h at room temperature, the mixture was diluted with EtOAc, phosphoric acid (0.1 M), and brine. The organic phase was separated, washed with brine, and dried over Na₂SO₄. The organic solution was concentrated, and the residue was purified by silica gel chromatography (DCM/MeOH 10:1) to deliver the product as a white foam.

Yield: 0.16 g (73%)

ESI-MS: m/z = 469 [M+H]⁺

The following compound can be obtained accordingly:

(20) 4-(2-Fluoro-4-ethoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole

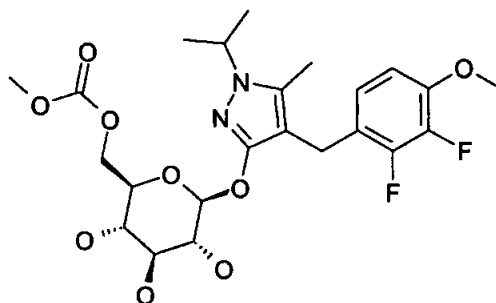


ESI-MS: m/z = 455 [M+H]⁺

The compounds (21) to (29) can be obtained by methods as described in this application or in the literature.

Example 4

(30a) 4-(2,3-Difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



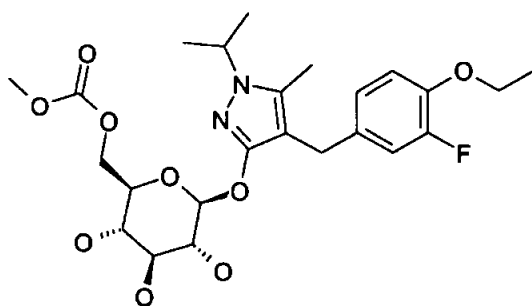
- 5 To an ice-cold solution of 4-(2,3-difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole (0.23 g, 0.50 mmol) in 2,4,6-trimethylpyridine (0.7 mL) was added methyl chloroformate (42 μL, 0.55 mmol). The reaction solution was warmed up in the ice-bath to room temperature and stirred over night. Then the solution was diluted with Et₂O, washed with aqueous HCl (1 M) and brine, and dried over MgSO₄. The solvent was
- 10 evaporated, and the residue was purified by chromatography on silica gel (DCM/MeOH 25:1->3:1) to afford the product as a white solid.

Yield: 0.15 g (56%)

ESI-MS: m/z = 517 [M+H]⁺

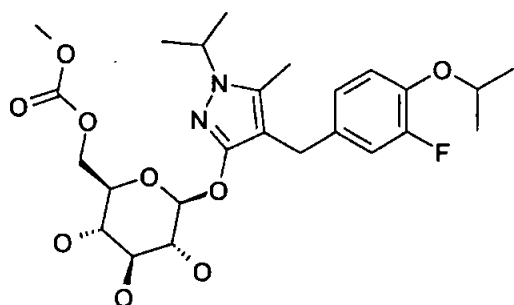
- 15 The following compounds can be obtained accordingly:

(31a) 4-(3-Fluoro-4-ethoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



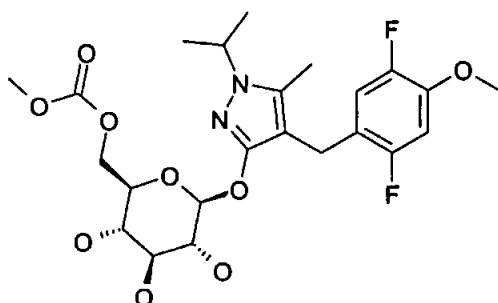
- 20 ESI-MS: m/z = 513 [M+H]⁺

(32a) 4-(3-Fluoro-4-isopropoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



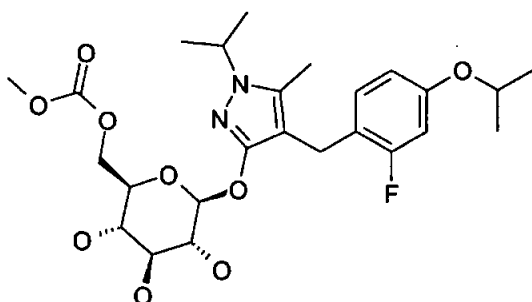
ESI-MS: $m/z = 527 [M+H]^+$

- 5 (33a) 4-(2,5-Difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



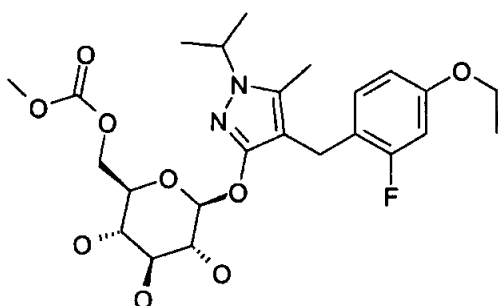
ESI-MS: $m/z = 517 [M+H]^+$

- 10 (34a) 4-(2-Fluoro-4-isopropoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



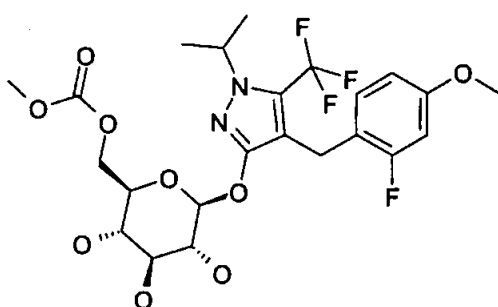
ESI-MS: $m/z = 527 [M+H]^+$

- 15 (35a) 4-(2-Fluoro-4-ethoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



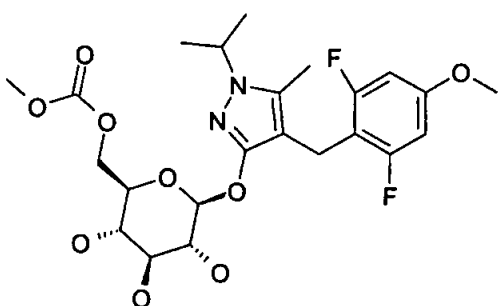
ESI-MS: $m/z = 513 [M+H]^+$

- (36a) 4-(2-fluoro-4-methoxy-benzyl)-1-isopropyl-5-trifluoromethyl-3-(6-O-methoxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



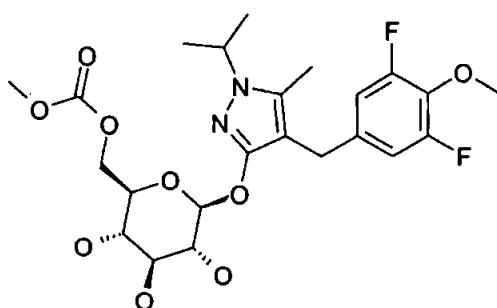
ESI-MS: $m/z = 553 [M+H]^+$

- (37a) 4-(2,6-Difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



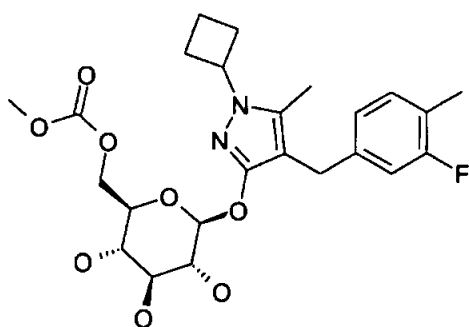
ESI-MS: $m/z = 517 [M+H]^+$

- (38a) 4-(3,5-Difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



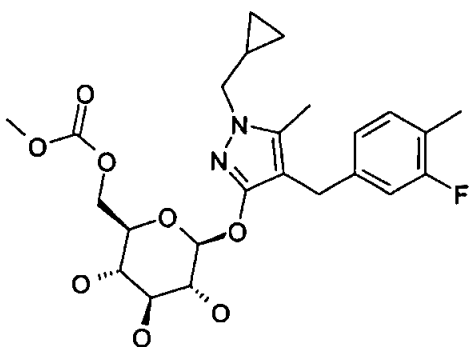
ESI-MS: $m/z = 517 [M+H]^+$

- 5 (39a) 1-Cyclobutyl-4-(3-fluoro-4-methyl-benzyl)-5-methyl-3-(6-O-methoxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



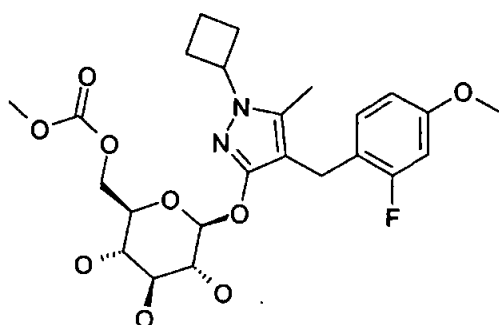
ESI-MS: $m/z = 495 [M+H]^+$

- 10 (40a) 1-Cyclopropylmethyl-4-(3-fluoro-4-methyl-benzyl)-5-methyl-3-(6-methoxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



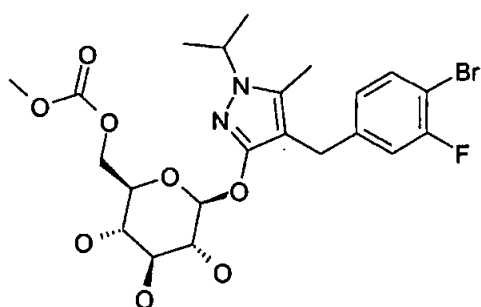
ESI-MS: $m/z = 495 [M+H]^+$

- 15 (41a) 1-Cyclobutyl-4-(2-fluoro-4-methoxy-benzyl)-5-methyl-3-(6-O-methoxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole

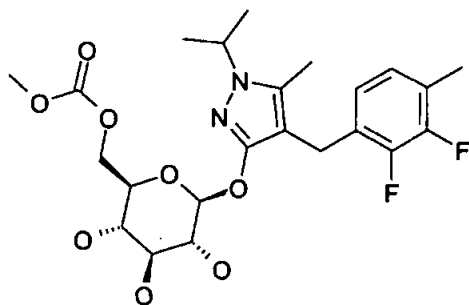


ESI-MS: $m/z = 511 [M+H]^+$

- 5 (42a) 4-(4-Bromo-3-fluoro-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole



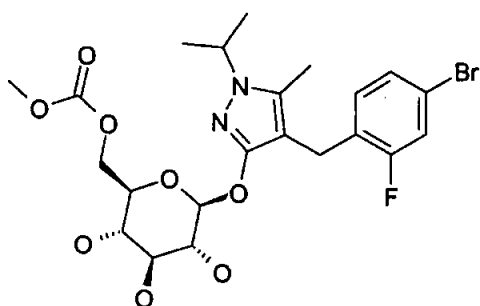
- (43a) 4-(2,3-Difluoro-4-methyl-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole



10

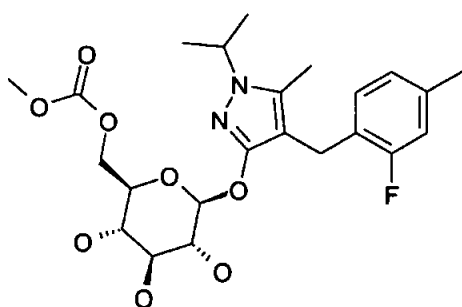
R_f 0.49 (silica gel, $CHCl_3/MeOH$ 10:1)

- (44a) 4-(4-Bromo-2-fluoro-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole



R_f 0.39 (silica gel, CH₂Cl₂/MeOH 19:1)

(45a) 4-(2-Fluoro-4-methyl-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole

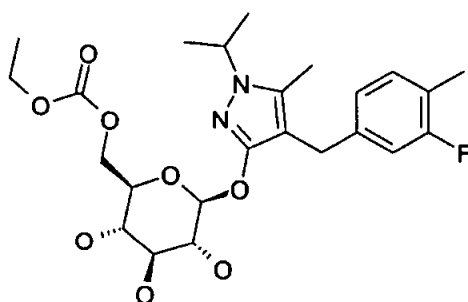


R_f 0.62 (silica gel, CH₂Cl₂/MeOH 9:1)

The compounds (30b), (31b), (32b), (33b), (34b), (35b), (36b), (37b), (38b), (39b), (40b), (41b), (42b), (43b), (44b) and (45b) are obtained analogously.

Example 5:

(46) 4-(3-Fluoro-4-methyl-benzyl)-1-isopropyl-5-methyl-3-(6-O-ethoxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



15

To an ice-cold solution of 4-(3-fluoro-4-methyl-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole (0.30 g, 0.70 mmol) in 2,4,6-trimethylpyridine (1 mL) was added methyl chloroformate (76 μL, 0.80 mmol). The reaction solution was warmed up in the ice-bath to room temperature and stirred over night. Then the solution was diluted with Et₂O, washed with aqueous HCl (1 M) and brine, and dried over MgSO₄. The solvent was evaporated and the residue was purified by chromatography on silica gel (DCM/MeOH 25:1- >3:1) to afford the product as a white solid.

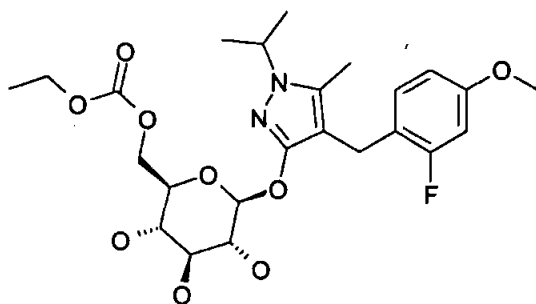
Yield: 0.23 g (66%)

ESI-MS: m/z = 497 [M+H]⁺

10

The following compounds can be obtained by analogy with the procedure described above:

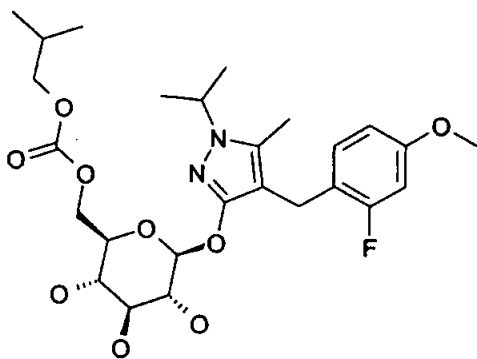
(47) 4-(2-Fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-ethoxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



15

ESI-MS: m/z = 513 [M+H]⁺

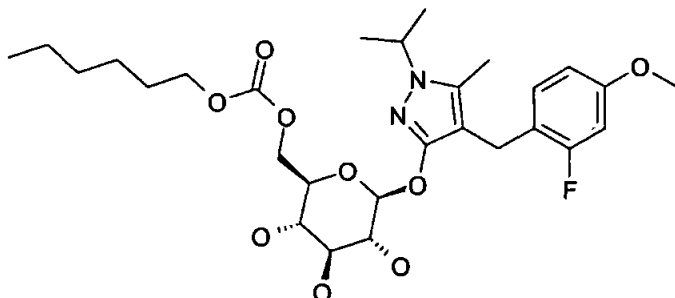
(48) 4-(2-Fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-isobutyloxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



20

ESI-MS: m/z = 541 [M+H]⁺

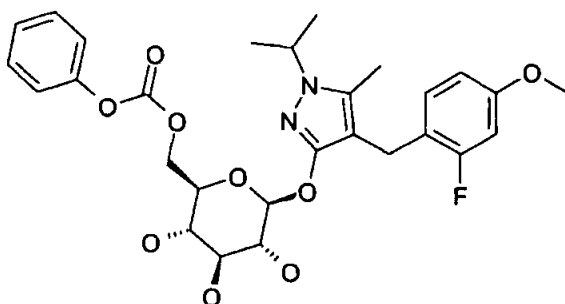
(49) 4-(2-Fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-hex-1-yloxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



ESI-MS: $m/z = 569 [M+H]^+$

5

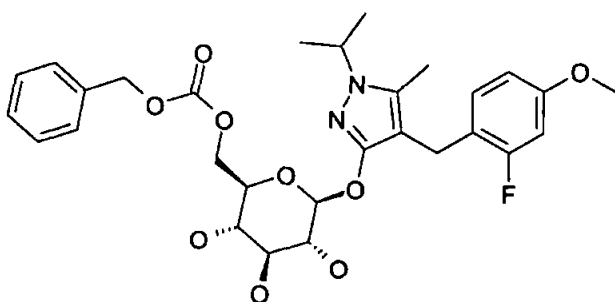
(50) 4-(2-Fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-phenoxy-carbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



ESI-MS: $m/z = 561 [M+H]^+$

10

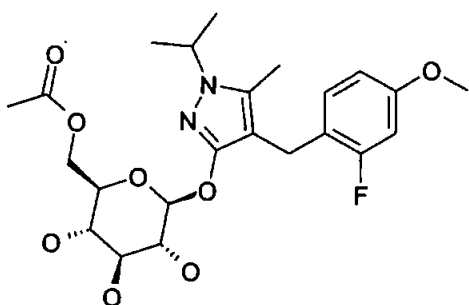
(51) 4-(2-Fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-benzyloxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



ESI-MS: $m/z = 575 [M+H]^+$

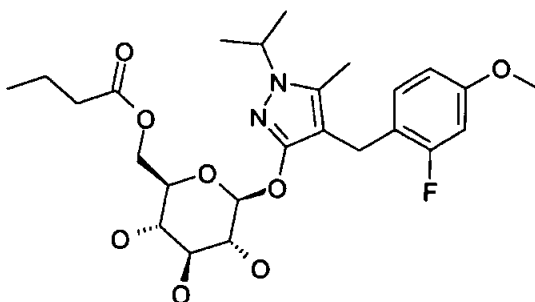
15

(52) 4-(2-Fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-acetyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



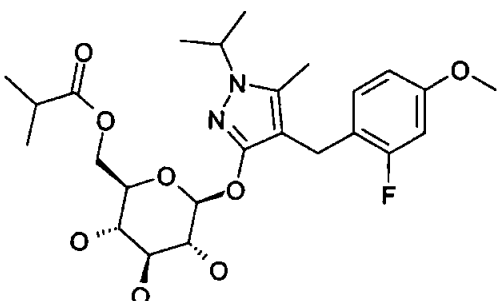
ESI-MS: $m/z = 483 [M+H]^+$

- 5 (53) 4-(2-Fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-propylcarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



ESI-MS: $m/z = 511 [M+H]^+$

- 10 (54) 4-(2-Fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-isopropylcarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole



ESI-MS: $m/z = 511 [M+H]^+$

- 15 (55) 4-(2-Fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-benzylcarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole

Patent Claims:

1. Method for preventing, slowing the progression of, delaying or treating a metabolic disorder selected from the group consisting of type 1 diabetes mellitus, type 2 diabetes mellitus, impaired glucose tolerance, hyperglycemia, postprandial hyperglycemia, overweight, obesity and metabolic syndrome in a patient in need thereof characterized in that
5 a pharmaceutical composition comprising a pyrazole-O-glucoside derivative selected from the group of compounds (1) to (29) consisting of

- (1) 4-(2,3-difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (2) 4-(2,5-difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (3) 4-(2,6-difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (4) 4-(3,5-difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (5) 1-cyclobutyl-4-(3-fluoro-4-methyl-benzyl)-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (6) 1-cyclopropylmethyl-4-(3-fluoro-4-methyl-benzyl)-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (7) 1-cyclobutyl-4-(2-fluoro-4-methoxy-benzyl)-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (8) 4-(3-chloro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (9) 4-(2-chloro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (10) 4-(4-bromo-3-fluoro-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (11) 4-(2,3-difluoro-4-methyl-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (12) 4-(2-fluoro-4-methyl-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (13) 4-(3-fluoro-4-ethoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;

- (14) 4-(4-ethynyl-benzyl)-1-isopropyl-5-methyl-3- β -D-glucopyranos-1-yloxy-1H-pyrazole;
- (15) 4-(3-fluoro-4-isopropoxy-benzyl)-1-isopropyl-5-methyl-3- β -D-glucopyranos-1-yloxy-1H-pyrazole;
- (16) 4-(2-fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3- β -D-glucopyranos-1-yloxy-1H-pyrazole;
- (17) 4-(2-fluoro-4-methoxy-benzyl)-1-isopropyl-5-trifluoromethyl-3- β -D-glucopyranos-1-yloxy-1H-pyrazole;
- (18) 4-(4-bromo-2-fluoro-benzyl)-1-isopropyl-5-methyl-3- β -D-glucopyranos-1-yloxy-1H-pyrazole;
- (19) 4-(2-fluoro-4-isopropoxy-benzyl)-1-isopropyl-5-methyl-3- β -D-glucopyranos-1-yloxy-1H-pyrazole;
- (20) 4-(2-fluoro-4-ethoxy-benzyl)-1-isopropyl-5-methyl-3- β -D-glucopyranos-1-yloxy-1H-pyrazole;
- (21) 4-(4-ethyl-benzyl)-1-isopropyl-5-trifluoromethyl-3- β -D-glucopyranos-1-yloxy-1H-pyrazole;
- (22) 4-(4-bromo-benzyl)-1-isopropyl-5-trifluoromethyl-3- β -D-glucopyranos-1-yloxy-1H-pyrazole;
- (23) 4-(4-ethyl-benzyl)-1-cyclobutyl-5-trifluoromethyl-3- β -D-glucopyranos-1-yloxy-1H-pyrazole;
- (24) 4-(4-ethyl-benzyl)-1-(2-fluoro-1-fluoromethyl-ethyl)-5-trifluoromethyl-3- β -D-glucopyranos-1-yloxy-1H-pyrazole;
- (25) 4-(3-fluoro-4-methoxy-benzyl)-1-isopropyl-5-trifluoromethyl-3- β -D-glucopyranos-1-yloxy-1H-pyrazole;
- (26) 4-(3-fluoro-4-methyl-benzyl)-1-isopropyl-5-methyl-3- β -D-glucopyranos-1-yloxy-1H-pyrazole;
- (27) 4-(2,3-difluoro-4-isopropoxy-benzyl)-1-isopropyl-5-methyl-3- β -D-glucopyranos-1-yloxy-1H-pyrazole;
- (28) 4-(3-fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3- β -D-glucopyranos-1-yloxy-1H-pyrazole;
- (29) 4-(4-ethyl-benzyl)-1-isopropyl-5-methyl-3- β -D-glucopyranos-1-yloxy-1H-pyrazole;

or a prodrug thereof wherein one or more hydroxyl groups of the β -D-glucopyranosyl group are acylated with groups selected from (C₁₋₁₈-alkyl)carbonyl, (C₁₋₁₈-alkyl)oxycarbonyl,

phenylcarbonyl, phenyl-(C₁₋₃-alkyl)-carbonyl, phenyloxycarbonyl and phenyl-(C₁₋₃-alkyl)-oxycarbonyl, or a pharmaceutically acceptable salt thereof;

is administered.

5

2. Method for improving glycemic control and/or for reducing of fasting plasma glucose, of postprandial plasma glucose and/or of glycosylated hemoglobin HbA1c in a patient in need thereof characterized in that a pharmaceutical composition comprising a pyrazole-O-glucoside derivative selected from the group of compounds (1) to (29), or a prodrug thereof, or a pharmaceutically acceptable salt thereof, defined as in claim 1 is administered.

3. Method for preventing, slowing, delaying or reversing progression from impaired glucose tolerance, insulin resistance and/or from metabolic syndrome to type 2 diabetes mellitus in a patient in need thereof characterized in that a pharmaceutical composition comprising a pyrazole-O-glucoside derivative selected from the group of compounds (1) to (29), or a prodrug thereof, or a pharmaceutically acceptable salt thereof, defined as in claim 1 is administered.

4. Method for preventing, slowing the progression of, delaying or treating of a condition or disorder selected from the group consisting of complications of diabetes mellitus such as cataracts and micro- and macrovascular diseases, such as nephropathy, retinopathy, neuropathy, tissue ischaemia, arteriosclerosis, myocardial infarction, stroke and peripheral arterial occlusive disease, in a patient in need thereof characterized in that a pharmaceutical composition comprising a pyrazole-O-glucoside derivative selected from the group of compounds (1) to (29), or a prodrug thereof, or a pharmaceutically acceptable salt thereof, defined as in claim 1 is administered.

5. Method for reducing the weight or preventing an increase of the weight or facilitating a reduction of the weight in a patient in need thereof characterized in that a pharmaceutical composition comprising a pyrazole-O-glucoside derivative selected from the group of compounds (1) to (29), or a prodrug thereof, or a pharmaceutically acceptable salt thereof, defined as in claim 1 is administered.

6. Method for preventing, slowing, delaying or treating the degeneration of pancreatic beta cells and/or the decline of the functionality of pancreatic beta cells and/or for improving

and/or restoring the functionality of pancreatic beta cells and/or restoring the functionality of pancreatic insulin secretion in a patient in need thereof characterized in that a pharmaceutical composition comprising a pyrazole-O-glucoside derivative selected from the group of compounds (1) to (29), or a prodrug thereof, or a pharmaceutically acceptable salt thereof, defined as in claim 1 is administered.

7. Method for maintaining and/or improving the insulin sensitivity and/or for treating or preventing hyperinsulinemia and/or insulin resistance in a patient in need thereof characterized in that a pharmaceutical composition comprising a pyrazole-O-glucoside derivative selected from the group of compounds (1) to (29), or a prodrug thereof, or a pharmaceutically acceptable salt thereof, defined as in claim 1 is administered.

8. Method according to one or more of the claims 1 to 7 characterized in that a pharmaceutical composition comprising an amount of 1 mg to 1000 mg of a pyrazole-O-glucoside derivative selected from the group of compounds (1) to (29), or a prodrug thereof, or a pharmaceutically acceptable salt thereof, defined as in claim 1 is administered per day with respect to an adult patient.

9. Method according to one or more of the claims 1 to 8 wherein the patient is an individual diagnosed of one or more of the conditions selected from the group consisting of overweight, obesity, visceral obesity and abdominal obesity.

10. Method according to one or more of the claims 1 to 8 wherein the patient is an individual who shows one, two or more of the following conditions:

- (a) a fasting blood glucose or serum glucose concentration greater than 110 mg/dL, in particular greater than 125 mg/dL;
- (b) a postprandial plasma glucose equal to or greater than 140 mg/dL;
- (c) an HbA1c value equal to or greater than 6.5 %, in particular equal to or greater than 8.0 %.

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11. Method according to one or more of the claims 1 to 8 wherein the patient is an individual wherein one, two, three or more of the following conditions are present:

- (a) obesity, visceral obesity and/or abdominal obesity,
- (b) triglyceride blood level $\geq$ 150 mg/dL,

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- 101
- (c) HDL-cholesterol blood level < 40 mg/dL in female patients and < 50 mg/dL in male patients,
 - (d) a systolic blood pressure $\geq$ 130 mm Hg and a diastolic blood pressure $\geq$ 85 mm Hg,
 - 5 (e) a fasting blood glucose level $\geq$ 110 mg/dL.

12. Method according to one or more of the claims 1 to 11 wherein the patient is an individual for whom the treatment with metformin is contraindicated and/or who has an
10 intolerance against metformin at therapeutic doses.

13. Method according to one or more of the claims 1 to 11 wherein the patient is an individual with insufficient glycemic control despite treatment with one or more antidiabetic drugs.
15

14. Method according to one or more of the claims 1 to 13 wherein the pyrazole-O-glucoside derivative is a prodrug selected from the group of compounds (1) to (29) defined as in claim 1, wherein the hydrogen atom of the hydroxyl group in 6-position of the β -D-glucopyranosyl-group is replaced by a group selected from among (C₁₋₃-alkyl)carbonyl, (C₁₋₆-alkyl)oxycarbonyl, phenyloxycarbonyl, benzyloxycarbonyl and benzylcarbonyl, or a
20 pharmaceutically acceptable salt thereof.

15. Method according to claim 14 wherein the prodrug of a pyrazole-O-glucoside derivative is selected from the group of compounds (30a) to (45a), (30b) to (45b) and (46) to (63) defined as in claim 20 and 21, or a pharmaceutically acceptable salt thereof, or from the
25 group of compounds (64) to (73)

- (64) 4-(3-fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (65) 4-(4-ethyl-benzyl)-1-isopropyl-5-trifluoromethyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (66) 4-(4-bromo-benzyl)-1-isopropyl-5-trifluoromethyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (67) 4-(4-ethyl-benzyl)-1-cyclobutyl-5-trifluoromethyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;

- (68) 4-(4-ethyl-benzyl)-1-(2-fluoro-1-fluoromethyl-ethyl)-5-trifluoromethyl-3-(6-O-methoxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole;
- (69) 4-(3-fluoro-4-methoxy-benzyl)-1-isopropyl-5-trifluoromethyl-3-(6-O-methoxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole;
- (70) 4-(3-fluoro-4-methyl-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole;
- (71) 4-(4-isopropoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole;
- (72) 4-(2-fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole;
- (73) 4-(4-ethyl-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole;

or a pharmaceutically acceptable salt thereof.

- 5 16. Use of a pyrazole-O-glucoside derivative selected from the group of compounds (1) to (29), or a prodrug thereof, or a pharmaceutically acceptable salt thereof, defined as in claim 1 for the manufacture of a medicament for a therapeutic method according to one or more of the claims 1 to 15.

- 10 17. Medicament or pharmaceutical composition for use in a method according to one or more of the claims 1 to 15 comprising a therapeutically or prophylactically effective amount of a pyrazole-O-glucoside derivative selected from the group of compounds (1) to (29), or a prodrug thereof, or a pharmaceutically acceptable salt thereof, defined as in claim 1.

18. Pyrazole-O-glucoside derivative selected from the group consisting of:

- (1) 4-(2,3-difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (2) 4-(2,5-difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (3) 4-(2,6-difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
- (4) 4-(3,5-difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-

- glucopyranos-1-yloxy-1H-pyrazole;
- (5) 1-cyclobutyl-4-(3-fluoro-4-methyl-benzyl)-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
 - (6) 1-cyclopropylmethyl-4-(3-fluoro-4-methyl-benzyl)-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
 - (7) 1-cyclobutyl-4-(2-fluoro-4-methoxy-benzyl)-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
 - (8) 4-(3-chloro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
 - (9) 4-(2-chloro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
 - (10) 4-(4-bromo-3-fluoro-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
 - (11) 4-(2,3-difluoro-4-methyl-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
 - (12) 4-(2-fluoro-4-methyl-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
 - (13) 4-(3-fluoro-4-ethoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
 - (14) 4-(4-ethinyl-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
 - (15) 4-(3-fluoro-4-isopropoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
 - (17) 4-(2-fluoro-4-methoxy-benzyl)-1-isopropyl-5-trifluoromethyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
 - (18) 4-(4-bromo-2-fluoro-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
 - (19) 4-(2-fluoro-4-isopropoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;
 - (20) 4-(2-fluoro-4-ethoxy-benzyl)-1-isopropyl-5-methyl-3-β-D-glucopyranos-1-yloxy-1H-pyrazole;

or a prodrug thereof wherein one or more hydroxyl groups of the β-D-glucopyranosyl group are acylated with groups selected from (C₁₋₁₈-alkyl)carbonyl, (C₁₋₁₈-alkyl)oxycarbonyl,

phenylcarbonyl, phenyl-(C₁₋₃-alkyl)-carbonyl, phenyloxycarbonyl and phenyl-(C₁₋₃-alkyl)-oxycarbonyl, or a pharmaceutically acceptable salt thereof.

19. Pyrazole-O-glucoside derivative according to claim 18 characterized in that it is a
5 prodrug, wherein the hydrogen atom of the hydroxyl group in 6-position of the β -D-glucopyranosyl-group is replaced by a group selected from among (C₁₋₃-alkyl)carbonyl, (C₁₋₆-alkyl)oxycarbonyl, phenyloxycarbonyl, benzyloxycarbonyl and benzylcarbonyl, or a pharmaceutically acceptable salt thereof.
- 10 20. Pyrazole-O-glucoside derivative according to claim 19 selected from the group consisting of
- (30a) 4-(2,3-difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
 - (30b) 4-(2,3-difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
 - (31a) 4-(3-fluoro-4-ethoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
 - (31b) 4-(3-fluoro-4-ethoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
 - (32a) 4-(3-fluoro-4-isopropoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
 - (32b) 4-(3-fluoro-4-isopropoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
 - (33a) 4-(2,5-difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
 - (33b) 4-(2,5-difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
 - (34a) 4-(2-fluoro-4-isopropoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
 - (34b) 4-(2-fluoro-4-isopropoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
 - (35a) 4-(2-fluoro-4-ethoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
 - (35b) 4-(2-fluoro-4-ethoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;

- (36a) 4-(2-fluoro-4-methoxy-benzyl)-1-isopropyl-5-trifluoromethyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (36b) 4-(2-fluoro-4-methoxy-benzyl)-1-isopropyl-5-trifluoromethyl-3-(6-O-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (37a) 4-(2,6-difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (37b) 4-(2,6-difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (38a) 4-(3,5-difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (38b) 4-(3,5-difluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (39a) 1-cyclobutyl-4-(3-fluoro-4-methyl-benzyl)-5-methyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (39b) 1-cyclobutyl-4-(3-fluoro-4-methyl-benzyl)-5-methyl-3-(6-O-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (40a) 1-cyclopropylmethyl-4-(3-fluoro-4-methyl-benzyl)-5-methyl-3-(6-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (40b) 1-cyclopropylmethyl-4-(3-fluoro-4-methyl-benzyl)-5-methyl-3-(6-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (41a) 1-cyclobutyl-4-(2-fluoro-4-methoxy-benzyl)-5-methyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (41b) 1-cyclobutyl-4-(2-fluoro-4-methoxy-benzyl)-5-methyl-3-(6-O-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (42a) 4-(4-bromo-3-fluoro-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (42b) 4-(4-bromo-3-fluoro-benzyl)-1-isopropyl-5-methyl-3-(6-O-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (43a) 4-(2,3-difluoro-4-methyl-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (43b) 4-(2,3-difluoro-4-methyl-benzyl)-1-isopropyl-5-methyl-3-(6-O-ethoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (44a) 4-(4-bromo-2-fluoro-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl- β -D-glucopyranos-1-yloxy)-1H-pyrazole;
- (44b) 4-(4-bromo-2-fluoro-benzyl)-1-isopropyl-5-methyl-3-(6-O-ethoxycarbonyl- β -

- D-glucopyranos-1-yloxy)-1H-pyrazole;
- (45a) 4-(2-fluoro-4-methyl-benzyl)-1-isopropyl-5-methyl-3-(6-O-methoxycarbonyl-
β-D-glucopyranos-1-yloxy)-1H-pyrazole;
- (45b) 4-(2-fluoro-4-methyl-benzyl)-1-isopropyl-5-methyl-3-(6-O-ethoxycarbonyl-β-
D-glucopyranos-1-yloxy)-1H-pyrazole;

or pharmaceutically acceptable salts thereof.

5 21. Pyrazole-O-glucoside derivative selected from the group consisting of:

- (46) 4-(3-Fluoro-4-methyl-benzyl)-1-isopropyl-5-methyl-3-(6-O-ethoxycarbonyl-
β-D-glucopyranos-1-yloxy)-1H-pyrazole;
- (47) 4-(2-Fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-ethoxycarbonyl-
β-D-glucopyranos-1-yloxy)-1H-pyrazole;
- (48) 4-(2-Fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-
isobutyloxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole;
- (49) 4-(2-Fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-hex-1-
yloxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole;
- (50) 4-(2-Fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-
phenoxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole;
- (51) 4-(2-Fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-
benzyloxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole;
- (52) 4-(2-Fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-acetyl-β-D-
glucopyranos-1-yloxy)-1H-pyrazole;
- (53) 4-(2-Fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-propylcarbonyl-
β-D-glucopyranos-1-yloxy)-1H-pyrazole;
- (54) 4-(2-Fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-
isopropylcarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole;
- (55) 4-(2-Fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-benzylcarbonyl-
β-D-glucopyranos-1-yloxy)-1H-pyrazole;
- (56) 4-(4-ethyl-benzyl)-1-isopropyl-5-trifluoromethyl-3-(6-O-ethoxycarbonyl-β-D-
glucopyranos-1-yloxy)-1H-pyrazole;
- (57) 4-(4-bromo-benzyl)-1-isopropyl-5-trifluoromethyl-3-(6-O-ethoxycarbonyl-β-
D-glucopyranos-1-yloxy)-1H-pyrazole;

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- (58) 4-(4-ethyl-benzyl)-1-cyclobutyl-5-trifluoromethyl-3-(6-O-ethoxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole;
- (59) 4-(4-ethyl-benzyl)-1-(2-fluoro-1-fluoromethyl-ethyl)-5-trifluoromethyl-3-(6-O-ethoxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole;
- (60) 4-(3-fluoro-4-methoxy-benzyl)-1-isopropyl-5-trifluoromethyl-3-(6-O-ethoxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole;
- (61) 4-(4-isopropoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-ethoxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole;
- (62) 4-(3-fluoro-4-methoxy-benzyl)-1-isopropyl-5-methyl-3-(6-O-ethoxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole;
- (63) 4-(4-ethyl-benzyl)-1-isopropyl-5-methyl-3-(6-O-ethoxycarbonyl-β-D-glucopyranos-1-yloxy)-1H-pyrazole;

or pharmaceutically acceptable salts thereof.

- 5 22. A pharmaceutical composition comprising at least one pyrazole-O-glucoside derivative of claim 18, 19, 20 or 21, or a pharmaceutically acceptable salt thereof.

Métodos para prevenir y tratar trastornos metabólicos y nuevos derivados de pirazol-O-glucósido

Campo técnico de la invención

- 5 La invención se refiere a métodos
- para prevenir, frenar la progresión, retrasar o tratar un trastorno metabólico;
 - para mejorar el control glucémico y/o para reducir la glucosa plasmática en ayunas, de glucosa plasmática posprandial y/o de hemoglobina HbA1c glicosilada;
 - para prevenir, frenar, retrasar o revertir la progresión desde la tolerancia alterada a
- 10 la glucosa, la resistencia a la insulina y/o desde el síndrome metabólico hasta de la diabetes mellitus de tipo 2;
- para prevenir, frenar la progresión, retrasar o tratar un trastorno o afección seleccionado del grupo que consiste en complicaciones de la diabetes mellitus;
 - para reducir el peso o prevenir un aumento de peso o facilitar una reducción de
- 15 peso;
- para prevenir o tratar la degeneración de células beta pancreáticas y/o para mejorar y/o restablecer la funcionalidad de células beta pancreáticas y/o restablecer la funcionalidad de la secreción de insulina pancreática;
 - mantener y/o mejorar la sensibilidad a la insulina y/o para tratar o prevenir la
- 20 hiperinsulinemia y/o la resistencia a la insulina,
- en pacientes que lo necesiten, mediante la administración de una composición farmacéutica que comprende un derivado de pirazol-O-glucósido seleccionado del grupo de compuestos (1) a (29), como se define a continuación, o su profármaco, o su sal farmacéuticamente aceptable. Además, la presente invención se refiere al uso de
- 25 un derivado de pirazol-O-glucósido según esta invención, para preparar una composición farmacéutica, y a estos medicamentos y composiciones farmacéuticas.
- Además, la presente invención se refiere a nuevos derivados de pirazol-O-glucósido, como se define a continuación, o sus profármacos, o sus sales farmacéuticamente aceptables.
- 30 La presente invención también se refiere a composiciones farmacéuticas que comprenden al menos uno de los derivados de pirazol-O-glucósido, como se define a continuación, o sus profármacos, o sus sales farmacéuticamente aceptables.

Antecedentes de la invención

La solicitud de patente europea EP 1338603 A1 describe nuevos derivados de pirazol-O-glucósido. Los derivados de pirazol-O-glucósido se proponen como inductores de la secreción de azúcar urinaria y como medicamentos en el tratamiento de la diabetes.

5 La filtración renal y la recaptación de glucosa contribuyen, entre otros mecanismos, a mantener en estado estable la concentración de la glucosa plasmática y, por tanto, pueden servir como diana antidiabética. La recaptación de glucosa filtrada a través de las células epiteliales del riñón se realiza mediante cotransportadores de glucosa dependientes de sodio (SGLT) que se encuentran en las membranas de borde
10 piloso en los túbulos proximales a lo largo del gradiente de sodio ⁽¹⁾. Existen al menos tres isoformas de SGLT que se diferencian en su patrón de expresión, así como en sus propiedades físico-químicas ⁽²⁾. El SGLT2 se expresa exclusivamente en el riñón ⁽³⁾, mientras que SGLT1 que se expresa además en otros tejidos, como el intestino, colon, músculo esquelético y cardíaco ^(4;5). Se ha descubierto que el SGLT3 es un
15 detector de glucosa en células intersticiales del intestino, sin ninguna función transportadora ⁽⁶⁾. Potencialmente, otros genes relacionados, pero aún no caracterizados, pueden contribuir también a la recaptación renal de la glucosa ^(7, 8, 9). En normoglucemia, la glucosa es completamente absorbida por los SGLT en el riñón, mientras que la capacidad de recaptación del riñón se satura a una concentración de
20 glucosa mayor que 10 mM, dando como resultado una glucosuria ("diabetes mellitus"). Esta concentración umbral puede disminuirse mediante la inhibición de SGLT2. Se ha demostrado en experimentos con el inhibidor de SGLT florizina que la inhibición de SGLT inhibe parcialmente la recaptación de glucosa desde el filtrado glomerular hacia la sangre, conduciendo a una disminución en la concentración de glucosa sanguínea y
25 a la glucosuria ^(10;11).

(1) Wright, E.M. (2001), Am. J. Renal Physiol., 280, F10-F18;

(2) Wright, E.M. et al. (2004), Pflugers Arch., 447(5):510-518;

(3) You, G. et al. (1995), J. Biol. Chem., 270(49), 29365-29371;

30 (4) Pajor A.M., Wright E.M. (1992), J. Biol. Chem., 267(6):3557-3560;

(5) Zhou, L. et al. (2003), J. Cell. Biochem., 90:339-346;

(6) Diez-Sampedro, A. et al. (2003), Proc. Natl. Acad. Sci. USA, 100(20), 11753-11758;

(7) Tabatabai, N.M. (2003), Kidney Int., 64, 1320-1330;

35 (8) Curtis, R.A.J. (2003), solicitud de patente de EEUU 2003/0054453;

- (9) Bruss, M. y Bonisch, H. (2001), Cloning and functional characterization of a new human sugar transporter in kidney (Genbank nº de registro AJ305237);
- (10) Rossetti, L. et al. (1987), J. Clin. Invest., 79, 1510-1515;
- (11) Gouvea, W.L. (1989), Kidney Int., 35(4):1041-1048.

5

La diabetes de tipo 2 es una enfermedad con una incidencia cada vez mayor que, debido a la alta frecuencia de las complicaciones, conduce a una significativa reducción de la esperanza de vida. Debido a las complicaciones microvasculares asociadas a la diabetes, la diabetes de tipo 2 es, en la actualidad, la causa más frecuente de la pérdida de visión de aparición en la vida adulta, insuficiencia renal, y amputaciones en el mundo industrializado. Además, la presencia de la diabetes de tipo 2 está asociada con un aumento de dos a cinco veces en el riesgo de enfermedad cardiovascular.

Después de sufrir la enfermedad durante mucho tiempo, la mayoría de los pacientes con diabetes de tipo 2 finalmente no responden a la terapia oral y se hacen dependientes de insulina, necesitando inyecciones diarias y múltiples medidas diarias de la glucosa.

El UKPDS (United Kingdom Prospective Diabetes Study; "Estudio prospectivo sobre la diabetes en el Reino Unido") demostró que un tratamiento intensivo con metformina, sulfonilureas o insulina producía sólo una mejora limitada del control glucémico (diferencia en HbA1c de aproximadamente 0,9%). Además, incluso en pacientes dentro del tratamiento intensivo, el control glucémico se deteriora significativamente a lo largo del tiempo, y esto se atribuyó al deterioro de la función de las células β . De manera importante, el tratamiento intensivo no se asoció con una reducción significativa en las complicaciones macrovasculares, es decir, acontecimientos cardiovasculares.

Por tanto, existe una necesidad médica no cubierta de fármacos con una buena eficacia con respecto al control glucémico, con respecto a las propiedades modificadoras de la enfermedad, y con respecto a la reducción de la morbilidad y mortalidad cardiovascular, mientras que al mismo tiempo muestren un perfil de seguridad mejorado.

Objetivo de la invención

El objetivo de la presente invención es proporcionar un método para prevenir, frenar la progresión, retrasar o tratar una enfermedad metabólica.

Otro objetivo de la presente invención es proporcionar un método para mejorar el control glucémico en un paciente que lo necesite.

Otro objetivo de la presente invención es proporcionar un método para prevenir, frenar o retrasar la progresión desde la tolerancia alterada a la glucosa, la resistencia a la insulina y/o el síndrome metabólico hasta la diabetes mellitus de tipo 2

Otro objetivo de la presente invención es proporcionar un método para prevenir, frenar la progresión, retrasar o tratar un trastorno o afección del grupo que consiste en complicaciones de la diabetes mellitus.

Otro objetivo de la presente invención es proporcionar un método para reducir el peso o prevenir un aumento de peso o facilitar una reducción de peso en un paciente que lo necesite.

Otros objetivos de la presente invención se refieren a nuevos usos de derivados de pirazol-O-glucósido según esta invención, incluyendo sus profármacos y sales farmacéuticamente aceptables.

Otro objetivo de la presente invención es proporcionar nuevos derivados de pirazol-O-glucósido y nuevos profármacos de los derivados de pirazol-O-glucósido que tienen un efecto inhibidor de bueno a muy bueno sobre el cotransportador de glucosa dependiente de sodio SGLT, en particular SGLT2, *in vitro* y/o *in vivo* y/o que tienen propiedades farmacológicas y/o farmacocinéticas y/o fisicoquímicas de buenas a muy buenas.

Otros objetivos de la presente invención serán obvios para los expertos en la técnica a partir de la anterior y posterior descripción y de los ejemplos.

Sumario de la invención

Dentro del alcance de la presente invención, ahora se ha descubierto, de forma sorprendente, que un derivado de pirazol-O-glucósido seleccionado del grupo de compuestos (1) a (29), o sus profármacos, o sus sales farmacéuticamente aceptables, como se define a continuación, puede utilizarse, de modo ventajoso, para prevenir, frenar la progresión, retrasar o tratar un trastorno metabólico, en particular para mejorar el control glucémico en pacientes. Esto abre nuevas posibilidades terapéuticas en el tratamiento y prevención de la diabetes mellitus de tipo 2, el sobrepeso, la obesidad, las complicaciones de la diabetes mellitus y de estados de enfermedad cercanos.

Por tanto, en un primer aspecto, la presente invención proporciona un método para prevenir, frenar la progresión, retrasar o tratar un trastorno metabólico

seleccionado del grupo que consiste en diabetes mellitus de tipo 1, diabetes mellitus de tipo 2, tolerancia alterada a la glucosa, hiperglucemia, hiperglucemia posprandial, sobrepeso, obesidad, incluyendo la obesidad de clase I, obesidad de clase II, obesidad de clase III, obesidad visceral y obesidad abdominal, y síndrome metabólico en un

5 paciente que lo necesite, que se caracteriza porque una composición farmacéutica que comprende un derivado de pirazol-O-glucósido seleccionado del grupo de compuestos (1) a (29), que consiste en

- (1) 4-(2,3-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (2) 4-(2,5-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (3) 4-(2,6-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (4) 4-(3,5-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (5) 1-ciclobutil-4-(3-fluoro-4-metilbencil)-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (6) 1-ciclopropilmetil-4-(3-fluoro-4-metilbencil)-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (7) 1-ciclobutil-4-(2-fluoro-4-metoxibencil)-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (8) 4-(3-cloro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (9) 4-(2-cloro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (10) 4-(4-bromo-3-fluorobencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (11) 4-(2,3-difluoro-4-metilbencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (12) 4-(2-fluoro-4-metilbencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (13) 4-(3-fluoro-4-etoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;

- (14) 4-(4-etilbencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (15) 4-(3-fluoro-4-isopropoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (16) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (17) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-trifluorometil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (18) 4-(4-bromo-2-fluorobencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (19) 4-(2-fluoro-4-isopropoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (20) 4-(2-fluoro-4-etoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (21) 4-(4-etilbencil)-1-isopropil-5-trifluorometil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (22) 4-(4-bromobencil)-1-isopropil-5-trifluorometil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (23) 4-(4-etilbencil)-1-ciclobutil-5-trifluorometil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (24) 4-(4-etilbencil)-1-(2-fluoro-1-fluorometiletil)-5-trifluorometil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (25) 4-(3-fluoro-4-metoxibencil)-1-isopropil-5-trifluorometil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (26) 4-(3-fluoro-4-metilbencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (27) 4-(2,3-difluoro-4-isopropoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (28) 4-(3-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (29) 4-(4-etilbencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;

o su profármaco, en los que uno o más grupos hidroxilo del grupo β-D-glucopiranosilo se acilan con grupos seleccionados de (alquil C₁₋₁₈)carbonilo, (alquil C₁₋₁₈)oxicarbonilo, fenilcarbonilo, fenil-(alquil C₁₋₃)-carbonilo, feniloxicarbonilo, y fenil-(alquil C₁₋₃)-

5 oxicarbonilo, o su sal farmacéuticamente aceptable, se administra.

Según otro aspecto de la invención, se proporciona un método para mejorar el control glucémico y/o para reducir la glucosa plasmática en ayunas, la glucosa plasmática posprandial y/o la hemoglobina HbA1c glicosilada en un paciente que lo necesite, que se caracteriza porque se administra una composición farmacéutica que comprende un derivado de pirazol-O-glucósido seleccionado del grupo de compuestos (1) a (29), o su profármaco, o su sal farmacéuticamente aceptable, definido como anterior y posteriormente.

Como mediante el uso de un compuesto según esta invención se obtiene una mejora del control glucémico en pacientes que lo necesiten, también pueden tratarse aquellos trastornos y/o enfermedades relacionados o provocados por un aumento en el nivel de glucosa sanguínea.

Por tanto, en otro aspecto, la invención proporciona un método para prevenir, frenar la progresión, retrasar o tratar un trastorno o afección seleccionado del grupo que consiste en complicaciones de la diabetes mellitus, como cataratas y enfermedades micro- y macrovasculares, como nefropatía, retinopatía, neuropatía, isquemia de tejidos, arteriosclerosis, infarto de miocardio, accidentes cerebrovasculares y enfermedad oclusiva arterial periférica, en un paciente que lo necesite, que se caracteriza porque se administra una composición farmacéutica que comprende un derivado de pirazol-O-glucósido seleccionado del grupo de compuestos (1) a (29), o su profármaco, o su sal farmacéuticamente aceptable, definido como anterior y posteriormente. La expresión "isquemia de tejidos" comprende, en particular, macroangiopatía diabética, microangiopatía diabética, curación dificultosa de heridas y úlcera diabética.

Los compuestos según esta invención también pueden tener valiosas propiedades modificadoras de enfermedad con respecto a enfermedades o trastornos relacionados con la tolerancia alterada a la glucosa, la resistencia a la insulina y/o el síndrome metabólico.

Por tanto, en otro aspecto de la presente invención, se proporciona un método para prevenir, frenar, retrasar o revertir la progresión desde la tolerancia alterada a la glucosa, la resistencia a la insulina y/o el síndrome metabólico hasta la diabetes mellitus de tipo 2 en un paciente que lo necesite, que se caracteriza porque se administra una composición farmacéutica que comprende un derivado de pirazol-O-glucósido seleccionado del grupo de compuestos (1) a (29), o su profármaco, o su sal farmacéuticamente aceptable, definido como anterior y posteriormente.

Mediante la administración de un compuesto según la invención los niveles excesivos de glucosa sanguínea no se convierten en formas de almacenamiento insolubles, como grasa, sino que se excretan a través de la orina del paciente. Por tanto, no se gana peso, e incluso se obtiene como resultado una reducción de peso.

5 Después de esto, otro aspecto de la invención proporciona un método para reducir el peso o prevenir un aumento de peso o facilitar una reducción de peso en un paciente que lo necesite, que se caracteriza porque se administra una composición farmacéutica que comprende un derivado de pirazol-O-glucósido seleccionado del grupo de compuestos (1) a (29), o su profármaco, o su sal farmacéuticamente
10 aceptable, definido como anterior y posteriormente.

El efecto farmacológico de los compuestos según la invención es independiente de la insulina. Por tanto, es posible una mejora del control glucémico sin un esfuerzo adicional de las células beta pancreáticas. Mediante la administración de un compuesto según esta invención puede retrasarse o prevenirse la degeneración de
15 las células beta y la disminución de la funcionalidad de las células beta como, por ejemplo, la apoptosis o necrosis de las células beta pancreáticas. Además, la funcionalidad de las células pancreáticas puede mejorarse o restablecerse, y puede aumentar el número y tamaño de las células beta pancreáticas. Puede demostrarse que el estado de diferenciación e hiperplasia de las células beta pancreáticas
20 alteradas por la hiperglucemia puede normalizarse mediante un tratamiento con un compuesto según la invención.

Por tanto, otro aspecto de la presente invención proporciona un método para prevenir, frenar, retrasar o tratar la degeneración de células beta pancreáticas y/o la disminución de la funcionalidad de las células beta pancreáticas y/o para mejorar y/o
25 restablecer la funcionalidad de las células beta pancreáticas y/o restablecer la funcionalidad de la secreción de insulina pancreática en un paciente que lo necesite, que se caracteriza porque se administra una composición farmacéutica que comprende un derivado de pirazol-O-glucósido seleccionado del grupo de compuestos (1) a (29), o su profármaco, o su sal farmacéuticamente aceptable, definido como
30 anterior y posteriormente.

Como resultado de esto, otro aspecto de la invención proporciona un método para mantener y/o mejorar la sensibilidad a la insulina y/o para tratar o prevenir la hiperinsulinemia y/o la resistencia a la insulina en un paciente que lo necesite, que se caracteriza porque se administra una composición farmacéutica que comprende un
35 derivado de pirazol-O-glucósido seleccionado del grupo de compuestos (1) a (29), o su

profármaco, o su sal farmacéuticamente aceptable, definido como anterior y posteriormente.

Otros aspectos de la presente invención se refieren al uso de un derivado de pirazol-O-glucósido seleccionado del grupo de compuestos (1) a (29), o su
5 profármaco, o su sal farmacéuticamente aceptable, definido como anterior y posteriormente, en el tratamiento o profilaxis de enfermedades o trastornos como se describe anterior y posteriormente.

Otros aspectos de la presente invención se refieren al uso de un derivado de pirazol-O-glucósido seleccionado del grupo de compuestos (1) a (29), o su
10 profármaco, o su sal farmacéuticamente aceptable, definido como anterior y posteriormente, para la fabricación de un medicamento para un método terapéutico como se describe anterior y posteriormente.

Además, otro aspecto de la presente invención se refiere a un medicamento o composición farmacéutica que comprende una cantidad terapéutica o
15 profilácticamente eficaz de un derivado de pirazol-O-glucósido seleccionado del grupo de compuestos (1) a (29), o su profármaco, o su sal farmacéuticamente aceptable, definido como anterior y posteriormente, para el tratamiento o la profilaxis de enfermedades o trastornos, descritos anterior y posteriormente.

Otro aspecto de la presente invención se refiere a nuevos derivados de pirazol-
20 O-glucósido seleccionados del grupo que consiste en:

- (1) 4-(2,3-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (2) 4-(2,5-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (3) 4-(2,6-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (4) 4-(3,5-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (5) 1-ciclobutil-4-(3-fluoro-4-metilbencil)-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (6) 1-ciclopropilmetil-4-(3-fluoro-4-metilbencil)-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (7) 1-ciclobutil-4-(2-fluoro-4-metoxibencil)-5-metil-3-β-D-glucopiranos-1-iloxi-

- 1H-pirazol;
- (8) 4-(3-cloro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
 - (9) 4-(2-cloro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
 - (10) 4-(4-bromo-3-fluorobencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
 - (11) 4-(2,3-difluoro-4-metilbencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
 - (12) 4-(2-fluoro-4-metilbencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
 - (13) 4-(3-fluoro-4-etoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
 - (14) 4-(4-etinilbencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
 - (15) 4-(3-fluoro-4-isopropoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
 - (17) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-trifluorometil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
 - (18) 4-(4-bromo-2-fluorobencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
 - (19) 4-(2-fluoro-4-isopropoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
 - (20) 4-(2-fluoro-4-etoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;

o su profármaco, en los que uno o más grupos hidroxilo del grupo β-D-glucopiranosilo se acilan con grupos seleccionados de (alquil C₁₋₁₈)carbonilo, (alquil C₁₋₁₈)oxicarbonilo, fenilcarbonilo, fenil-(alquil C₁₋₃)-carbonilo, feniloxicarbonilo, y fenil-(alquil C₁₋₃)-oxicarbonilo, o su sal farmacéuticamente aceptable.

Otro aspecto de la presente invención se refiere a nuevos profármacos de derivados de pirazol-O-glucósido seleccionados del grupo que consiste en:

- (46) 4-(3-fluoro-4-metilbencil)-1-isopropil-5-metil-3-(6-O-etoxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;

- (47) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-etoxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (48) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-isobutiloxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (49) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-hex-1-iloxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (50) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-fenoxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (51) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-benciloxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (52) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-acetil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (53) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-propilcarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (54) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-isopropilcarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (55) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-bencilcarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (56) 4-(4-etilbencil)-1-isopropil-5-trifluorometil-3-(6-O-etoxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (57) 4-(4-bromobencil)-1-isopropil-5-trifluorometil-3-(6-O-etoxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (58) 4-(4-etilbencil)-1-ciclobutil-5-trifluorometil-3-(6-O-etoxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (59) 4-(4-etilbencil)-1-(2-fluoro-1-fluorometiletil)-5-trifluorometil-3-(6-O-etoxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (60) 4-(3-fluoro-4-metoxibencil)-1-isopropil-5-trifluorometil-3-(6-O-etoxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (61) 4-(4-isopropoxibencil)-1-isopropil-5-metil-3-(6-O-etoxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (62) 4-(3-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-etoxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (63) 4-(4-etilbencil)-1-isopropil-5-metil-3-(6-O-etoxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;

o sus sales farmacéuticamente aceptables.

Otro aspecto de la presente invención se refiere a composiciones farmacéuticas que comprenden al menos un derivado de pirazol-O-glucósido según esta invención, o su sal farmacéuticamente aceptable.

5

Definiciones

La expresión "**índice de masa corporal**" o "**IMC**" de un paciente humano se define como el peso en kilogramos dividido entre el cuadrado de la altura en metros, de forma que el IMC tiene unidades de kg/m^2 .

10 El término "**sobrepeso**" se define como el trastorno en el que el individuo tiene un IMC de 25 kg/m^2 o mayor, y menor que 30 kg/m^2 . Los términos "sobrepeso" y "preobeso" se utilizan de forma intercambiable.

El término "**obesidad**" se define como el trastorno en el que el individuo tiene un IMC igual o mayor que 30 kg/m^2 . Según una definición de la OMS, el término
15 obesidad puede clasificarse como sigue: la expresión "obesidad de clase I" es el trastorno en el que el IMC es igual o mayor que 30 kg/m^2 , pero menor que 35 kg/m^2 ; la expresión "obesidad de clase II" es el trastorno en el que el IMC es igual o mayor que 35 kg/m^2 , pero menor que 40 kg/m^2 ; el término "obesidad de clase III" es el trastorno en el que el IMC es igual o mayor que 40 kg/m^2 .

20 La expresión "**obesidad visceral**" se define como el trastorno en el que se mide una proporción de cintura a cadera mayor o igual que 1,0 en hombres y 0,8 en mujeres. Define el riesgo de resistencia a la insulina y el desarrollo de prediabetes.

La expresión "**obesidad abdominal**" se define, normalmente, como el trastorno en el que la circunferencia de cintura es $> 102 \text{ cm}$ en hombres, y es $> 94 \text{ cm}$
25 en mujeres. Con respecto a la etnia japonesa o a pacientes japoneses, la obesidad abdominal puede definirse como una circunferencia de cintura $\geq 85 \text{ cm}$ en hombres y $\geq 90 \text{ cm}$ en mujeres (véase, por ejemplo, el comité de investigación para el diagnóstico del síndrome metabólico en Japón).

El término "**euglucemia**" se define como el trastorno en el que un sujeto tiene una concentración sanguínea de glucosa en ayunas dentro del intervalo normal, mayor
30 que 70 mg/dl ($3,89 \text{ mmol/l}$) y menor que 110 mg/dl ($6,11 \text{ mmol/l}$). La expresión "en ayunas" tiene el significado normal como término médico.

El término "**hiperglucemia**" se define como el trastorno en el que un sujeto tiene una concentración sanguínea de glucosa en ayunas por encima del intervalo

normal, mayor que 110 mg/dl (6,11 mmol/l). La expresión "en ayunas" tiene el significado normal como término médico.

La expresión "**hiperglucemia posprandial**" se define como el trastorno en el que un sujeto tiene una concentración sanguínea de glucosa o concentración sérica de glucosa posprandial a las 2 horas mayor que 200 mg/dl (11,11 mmol/l).

La expresión "**tolerancia alterada a la glucosa**" o "**IGT**" se define como el trastorno en el que un sujeto tiene una concentración sanguínea de glucosa en ayunas o una concentración sérica de glucosa en ayunas mayor que 110 mg/dl y menor que 126 mg/dl (7,00 mmol/l), o una concentración sanguínea de glucosa o concentración sérica de glucosa posprandial a las 2 horas mayor 140 mg/dl (7,78 mmol/l) y menor que 200 mg/dl (11,11 mmol/l). También se pretende que la expresión tolerancia alterada a la glucosa se aplique al trastorno de glucosa alterada en ayunas. La tolerancia anómala a la glucosa, es decir, la concentración sanguínea de glucosa o concentración sérica de glucosa posprandial a las 2 horas puede medirse como el nivel sanguíneo de azúcar en mg de glucosa por dl de plasma 2 horas después de ingerir 75 g de glucosa después del ayuno.

El término "**hiperinsulinemia**" se define como el trastorno en el que un sujeto tiene resistencia a la insulina, con o sin euglucemia, en el que la concentración sérica o plasmática de insulina en ayunas o posprandial se eleva por encima de la de los individuos delgados normales, sin resistencia a la insulina, que tienen un proporción de cintura a cadera < 1,0 (para hombres) o < 0,8 (para mujeres).

Las expresiones "sensibilización a la insulina", "mejora de la resistencia a la insulina" o "disminución de la resistencia a la insulina" son sinónimas y se utilizan de modo intercambiable.

La expresión "**resistencia a la insulina**" se define como un estado en el que se requieren unos niveles de insulina en la circulación en exceso de la respuesta normal a una carga de glucosa, para mantener el estado euglucémico (Ford E.S., *et al.*, JAMA., (2002), 287:356-359). Un método para determinar la resistencia a la insulina es el ensayo de tenaza euglucémico-hiperinsulinémico. La proporción de insulina a glucosa se determina dentro del alcance de una técnica combinada de infusión de insulina-glucosa. Se determina que existe una resistencia a la insulina si la absorción de glucosa está por debajo del 25º percentil de la población de fondo investigada (definición de la OMS). Un poco menos trabajosos que el ensayo de tenaza son los denominados modelos mínimos, en los que durante un ensayo de tolerancia a la glucosa intravenosa, las concentraciones de insulina y glucosa en la

sangre se miden a intervalos de tiempo fijos y, a partir de éstos, se calcula la resistencia a la insulina. En este método no es posible distinguir entre resistencia a la insulina hepática y periférica.

Además de la resistencia a la insulina, la respuesta a la terapia de un paciente con resistencia a la insulina, sensibilidad a la insulina e hiperinsulinemia puede cuantificarse mediante la evaluación de la puntuación de la "evaluación de la resistencia a la insulina en un modelo de homeostasis (HOMA-IR)", un indicador fiable de la resistencia a la insulina (Katsuki A., *et al.*, Diabetes Care, 2001, 24:362-365). También se hace referencia a métodos para la determinación del índice HOMA para la sensibilidad a la insulina (Matthews *et al.*, Diabetologia, 1985, 28:412-419), de la proporción de proinsulina intacta a insulina (Forst *et al.*, Diabetes, 2003, 52(supl.1):A459) y a un estudio de tenazas euglucémico. Además, los niveles plasmáticos de adiponectina pueden controlarse como sustituto potencial de la sensibilidad a la insulina. La estimación de la resistencia a la insulina mediante la puntuación del modelo de evaluación de la homeostasis (HOMA)-IR se calcula con la fórmula (Galvin P., *et al.*, Diabet. Med., 1992, 9:921-928):

$$\text{HOMA-IR} = [\text{insulina sérica en ayunas } (\mu\text{U/ml})] \times [\text{glucosa plasmática en ayunas } (\text{mmol/l})/22,5]$$

20

Como norma, se utilizan otros parámetros en la práctica clínica diaria para evaluar la resistencia a la insulina. Preferiblemente, se utiliza la concentración de triglicéridos del paciente, por ejemplo, puesto que unos niveles mayores de triglicéridos se correlacionan significativamente con la presencia de resistencia a la insulina.

25

Los pacientes con una predisposición para el desarrollo de IGT o de diabetes de tipo 2 son los que tiene euglucemia con hiperinsulinemia y son, por definición, resistentes a la insulina. Un paciente típico con resistencia a la insulina normalmente tiene sobrepeso o es obeso. Si puede detectarse resistencia a la insulina, ésta es una indicación particularmente fuerte de la presencia de prediabetes. Por tanto, puede que, para mantener la homeostasis de la glucosa, una persona necesite 2-3 veces más insulina que otra persona, sin que esto tenga ninguna importancia patológica directa.

30

Los métodos para investigar la **función de las células beta pancreáticas** son similares a los métodos anteriores con respecto a la sensibilidad a la insulina, hiperinsulinemia o resistencia a la insulina: Una mejora en la función de la células beta

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puede medirse, por ejemplo, determinando un índice HOMA para la función de las células beta (Matthews *et al.*, Diabetologia, 1985, 28:412-419), de la proporción de proinsulina intacta a insulina (Forst *et al.*, Diabetes, 2003, 52(supl.1):A459), de la secreción de insulina/péptido C después de un ensayo de tolerancia a la glucosa oral o un ensayo de tolerancia a comida, o empleando un estudio de tenaza hiperglucémico y/o un modelo mínimo después de un ensayo de tolerancia a la glucosa intravenoso con toma de muestras frecuentes (Stumvoll *et al.*, Eur. J. Clin. Invest., 2001, 31:380-381).

El término "**prediabetes**" es el trastorno en el que un individuo está predispuesto al desarrollo de la diabetes de tipo 2. La prediabetes extiende la definición de tolerancia alterada a la glucosa para incluir individuos con una glucosa sanguínea en ayunas dentro del intervalo normal alto ≥ 100 mg/dl (J. B. Meigs, *et al.*, Diabetes, 2003, 52:1475-1484) e hiperinsulinemia en ayunas (concentración plasmática de insulina elevada). La base científica y médica para identificar la prediabetes como amenaza grave para la salud se expone en un informe de opinión titulado "The Prevention or Delay of Type 2 Diabetes" emitido conjuntamente por the American Diabetes Association y the National Institute of Diabetes and Digestive and Kidney Diseases (Diabetes Care, 2002, 25:742-749).

Los individuos con probabilidad de tener resistencia a la insulina son los que tienen dos o más de los siguientes atributos: 1) sobrepeso u obesos, 2) hipertensión arterial, 3) hiperlipidemia, 4) uno o más parientes de primer grado con un diagnóstico de IGT o diabetes de tipo 2. La resistencia a la insulina puede confirmarse en estos individuos calculando la puntuación HOMA-IR. Para los objetivos de esta invención, la resistencia a la insulina se define como el trastorno clínico en el que el individuo tiene una puntuación HOMA-IR $> 4,0$, o una puntuación HOMA-IR por encima del límite superior normal, según la definición del laboratorio que realice los ensayos de glucosa e insulina.

La expresión "**diabetes de tipo 2**" se define como el trastorno en el que un sujeto tiene una concentración sanguínea de glucosa o concentración sérica de glucosa en ayunas mayor que 125 mg/dl (6,94 mmol/l). La medida de los valores de la glucosa sanguínea es un procedimiento convencional en los análisis médicos rutinarios. Si se realiza un ensayo de tolerancia a la glucosa, el nivel sanguíneo de azúcar de un diabético será mayor que 200 mg de glucosa por dl de plasma 2 horas después de ingerir 75 g de glucosa con el estómago vacío. En un ensayo de tolerancia a la glucosa se administran 75 g de glucosa por vía oral al paciente que se está

ensayando después de 10-12 horas de ayuno, y el nivel sanguíneo de azúcar se registra inmediatamente antes de ingerir la glucosa, y 1 y 2 horas después de ingerirla. En un sujeto sano, el nivel sanguíneo de azúcar antes de ingerir la glucosa estará entre 60 y 110 mg por dl de plasma, menor que 200 mg por dl 1 hora después de ingerir la glucosa, y menor que 140 mg por dl después de 2 horas. Si después de 2 horas el valor es entre 140 y 200 mg, esto se considera una tolerancia anómala a la glucosa.

La expresión "**etapa tardía de la diabetes mellitus de tipo 2**" incluye grandal pacientes con un fallo a fármacos secundario, una indicación para la terapia con insulina, y una progresión a complicaciones micro- y macrovasculares, por ejemplo, nefropatía diabética, enfermedad cardíaca coronaria (CHD).

El término "**HbA1c**" se refiere al producto de una glicación no enzimática de la cadena B de la hemoglobina. Su determinación es bien conocida por los expertos en la técnica. En el control del tratamiento de la diabetes mellitus, el valor de HbA1c tiene una importancia excepcional. Puesto que su producción depende esencialmente del nivel sanguíneo de azúcar y la vida de los eritrocitos, el HbA1c, en el sentido de una "memoria del azúcar sanguíneo", refleja los niveles sanguíneos medios de azúcar de las 4-6 semanas anteriores. Los pacientes diabéticos cuyo valor de HbA1c está coherentemente bien ajustado mediante un tratamiento intensivo de la diabetes (es decir, < 6,5 % de la hemoglobina total en la muestra), están significativamente mejor protegidos contra la microangiopatía diabética. Por ejemplo, la metformina, por sí misma, logra una mejora media en el valor de HbA1c en diabéticos del orden de 1,0 – 1,5 %. Esta reducción del valor de HbA1C no es suficiente en todos los diabéticos para lograr el intervalo diana deseado de < 6,5 % y preferiblemente < 6 % de HbA1c.

El "**síndrome metabólico**", también denominando "síndrome X" (cuando se utiliza en el contexto de un trastorno metabólico), también llamado "síndrome dismetabólico" es un síndrome complejo con la característica cardinal de presentar resistencia a la insulina (Laaksonen D.E., *et al.*, Am. J. Epidemiol., 2002, **156**:1070-1077). Según las líneas directrices de ATP III/NCEP (Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), *JAMA: Journal of the American Medical Association* (2001), **285**:2486-2497), se realiza un diagnóstico de síndrome metabólico cuando tres o más de los siguientes factores de riesgo están presentes:

1. Obesidad abdominal, definida como una circunferencia de cintura > 102 cm en hombres, y > 94 cm en mujeres; o con respecto a la etnia japonesa o pacientes japoneses, se define como una circunferencia de cintura ≥ 85 cm en hombres, y ≥ 90 cm en mujeres;
- 5 2. Triglicéridos: ≥ 150 mg/dl
3. Colesterol HDL < 40 mg/dl en hombres
4. Presión sanguínea $\geq 130/85$ mm Hg (SBP ≥ 130 o DBP ≥ 85)
5. Glucosa sanguínea en ayunas ≥ 110 mg/dl

Las definiciones de NCEP se han validado (Laaksonen D.E., *et al.*, Am. J. Epidemiol. (2002), 156:1070-1077). Los triglicéridos y el colesterol HDL en la sangre también pueden determinarse mediante métodos convencionales en el análisis médico y se describen, por ejemplo, en Thomas L. (editor): "Labor und Diagnose", TH-Books Verlagsgesellschaft mbH, Frankfurt/Main, 2000.

Según una definición utilizada habitualmente, se diagnostica **hipertensión** si la presión sanguínea sistólica (SBP) es mayor que 140 mm Hg, y la presión sanguínea diastólica (DBP) es mayor que 90 mm Hg. Si un paciente sufre diabetes manifiesta, en la actualidad se recomienda reducir la presión sanguínea sistólica a un nivel menor que 130 mm Hg, y reducir la presión sanguínea diastólica hasta un nivel menor que 80 mm Hg.

20 La expresión "tratar profilácticamente" y el término "prevenir" se utilizan de modo intercambiable.

Descripción detallada

Los aspectos según la presente invención, en particular los métodos y usos, se refieren a derivados de pirazol-O-glucósido seleccionados del grupo de compuestos (1) a (29) como se define anterior y posteriormente en la presente, o sus profármacos, o sus sales farmacéuticamente aceptables.

Preferiblemente, todos los grupos hidroxilo no están sustituidos, o sólo el grupo hidroxilo conectado al átomo de carbono en la 6ª posición del grupo β -D-glucopiranosilo está sustituido como se define. Los sustituyentes preferidos se seleccionan de (alquil C_{1-3})carbonilo, (alquil C_{1-6})oxicarbonilo, feniloxicarbonilo, benciloxicarbonilo y bencilcarbonilo. Los sustituyentes aún más preferidos se seleccionan de acetilo, metoxicarbonilo y etoxicarbonilo, en particular etoxicarbonilo.

Los profármacos preferidos se seleccionan del grupo que consiste en

- (30a) 4-(2,3-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-metoxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (30b) 4-(2,3-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-etoxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (31a) 4-(3-fluoro-4-etoxibencil)-1-isopropil-5-metil-3-(6-O-metoxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (31b) 4-(3-fluoro-4-etoxibencil)-1-isopropil-5-metil-3-(6-O-etoxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (32a) 4-(3-fluoro-4-isopropoxibencil)-1-isopropil-5-metil-3-(6-O-metoxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (32b) 4-(3-fluoro-4-isopropoxibencil)-1-isopropil-5-metil-3-(6-O-etoxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (33a) 4-(2,5-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-metoxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (33b) 4-(2,5-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-etoxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (34a) 4-(2-fluoro-4-isopropoxibencil)-1-isopropil-5-metil-3-(6-O-metoxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (34b) 4-(2-fluoro-4-isopropoxibencil)-1-isopropil-5-metil-3-(6-O-etoxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (35a) 4-(2-fluoro-4-etoxibencil)-1-isopropil-5-metil-3-(6-O-metoxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (35b) 4-(2-fluoro-4-etoxibencil)-1-isopropil-5-metil-3-(6-O-etoxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (36a) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-trifluorometil-3-(6-O-metoxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (36b) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-trifluorometil-3-(6-O-etoxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (37a) 4-(2,6-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-metoxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (37b) 4-(2,6-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-etoxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (38a) 4-(3,5-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-metoxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (38b) 4-(3,5-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-etoxicarbonil-β-D-

- glucopiranos-1-iloxi)-1H-pirazol;
- (39a) 1-ciclobutil-4-(3-fluoro-4-metilbencil)-5-metil-3-(6-O-metoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (39b) 1-ciclobutil-4-(3-fluoro-4-metilbencil)-5-metil-3-(6-O-etoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (40a) 1-ciclopropilmetil-4-(3-fluoro-4-metilbencil)-5-metil-3-(6-O-metoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (40b) 1-ciclopropilmetil-4-(3-fluoro-4-metilbencil)-5-metil-3-(6-O-etoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (41a) 1-ciclobutil-4-(2-fluoro-4-metoxibencil)-5-metil-3-(6-O-metoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (41b) 1-ciclobutil-4-(2-fluoro-4-metoxibencil)-5-metil-3-(6-O-etoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (42a) 4-(4-bromo-3-fluorobencil)-1-isopropil-5-metil-3-(6-O-metoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (42b) 4-(4-bromo-3-fluorobencil)-1-isopropil-5-metil-3-(6-O-etoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (43a) 4-(2,3-difluoro-4-metilbencil)-1-isopropil-5-metil-3-(6-O-metoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (43b) 4-(2,3-difluoro-4-metilbencil)-1-isopropil-5-metil-3-(6-O-etoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (44a) 4-(4-bromo-2-fluorobencil)-1-isopropil-5-metil-3-(6-O-metoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (44b) 4-(4-bromo-2-fluorobencil)-1-isopropil-5-metil-3-(6-O-etoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (45a) 4-(2-fluoro-4-metilbencil)-1-isopropil-5-metil-3-(6-O-metoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (45b) 4-(2-fluoro-4-metilbencil)-1-isopropil-5-metil-3-(6-O-etoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;

o sus sales farmacéuticamente aceptables.

Además, otros profármacos preferidos se seleccionan del grupo que consiste en los compuestos (46) a (63), o sus sales farmacéuticamente aceptables, como se

5 define anterior y posteriormente en la presente.

Otros profármacos preferidos se seleccionan del grupo que consiste en los compuestos (64) a (73)

- (64) 4-(3-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-metoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (65) 4-(4-etilbencil)-1-isopropil-5-trifluorometil-3-(6-O-metoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (66) 4-(4-bromobencil)-1-isopropil-5-trifluorometil-3-(6-O-metoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (67) 4-(4-etilbencil)-1-ciclobutil-5-trifluorometil-3-(6-O-metoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (68) 4-(4-etilbencil)-1-(2-fluoro-1-fluorometiletil)-5-trifluorometil-3-(6-O-metoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (69) 4-(3-fluoro-4-metoxibencil)-1-isopropil-5-trifluorometil-3-(6-O-metoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (70) 4-(3-fluoro-4-metilbencil)-1-isopropil-5-metil-3-(6-O-metoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (71) 4-(4-isopropoxibencil)-1-isopropil-5-metil-3-(6-O-metoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (72) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-metoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (73) 4-(4-etilbencil)-1-isopropil-5-metil-3-(6-O-metoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;

5 o su sal farmacéuticamente aceptable.

Según una primera realización preferida, los aspectos según la invención, en particular los métodos y usos, se refieren a

- (1) 4-(2,3-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;

10 o su profármaco, en el que el grupo hidroxilo conectado al átomo de carbono en la 6ª posición del grupo β-D-glucopiranosilo está sustituido con un sustituyente seleccionado de (alquil C₁₋₃)carbonilo, (alquil C₁₋₆)oxycarbonilo, feniloxycarbonilo,

benciloxycarbonilo y bencilcarbonilo, en particular seleccionado de acetilo, metoxycarbonilo y etoxycarbonilo; por ejemplo, el compuesto (30a) y (30b).

Según una segunda realización preferida, los aspectos según la invención, en particular los métodos y usos, se refieren a

5

(11) 4-(2,3-difluoro-4-metilbencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;

o su profármaco, en el que el grupo hidroxilo conectado al átomo de carbono en la 6ª posición del grupo β-D-glucopiranosilo está sustituido con un sustituyente seleccionado de (alquil C₁₋₃)carbonilo, (alquil C₁₋₆)oxycarbonilo, feniloxycarbonilo, benciloxycarbonilo y bencilcarbonilo, en particular seleccionado de acetilo, metoxycarbonilo y etoxycarbonilo; por ejemplo, el compuesto (43a) y (43b).

10

Según una tercera realización preferida, los aspectos según la invención, en particular los métodos y usos, se refieren a

(12) 4-(2-fluoro-4-metilbencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;

o su profármaco, en el que el grupo hidroxilo conectado al átomo de carbono en la 6ª posición del grupo β-D-glucopiranosilo está sustituido con un sustituyente seleccionado de (alquil C₁₋₃)carbonilo, (alquil C₁₋₆)oxycarbonilo, feniloxycarbonilo, benciloxycarbonilo y bencilcarbonilo, en particular seleccionado de acetilo, metoxycarbonilo y etoxycarbonilo; por ejemplo, el compuesto (45a) y (45b).

15

Según una cuarta realización preferida, los aspectos según la invención, en particular los métodos y usos, se refieren a

20

(16) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;

o su profármaco, en el que el grupo hidroxilo conectado al átomo de carbono en la 6ª posición del grupo β-D-glucopiranosilo está sustituido con un sustituyente seleccionado de (alquil C₁₋₃)carbonilo, (alquil C₁₋₆)oxycarbonilo, feniloxycarbonilo, benciloxycarbonilo y bencilcarbonilo, en particular seleccionado de acetilo, metoxycarbonilo y etoxycarbonilo; por ejemplo, el compuesto (47) y (72).

25

Según una quinta realización preferida, los aspectos según la invención, en particular los métodos y usos, se refieren a

(20) 4-(2-fluoro-4-etoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;

5 o su profármaco, en el que el grupo hidroxilo conectado al átomo de carbono en la 6ª posición del grupo β-D-glucopiranosilo está sustituido con un sustituyente seleccionado de (alquil C₁₋₃)carbonilo, (alquil C₁₋₆)oxicarbonilo, feniloxicarbonilo, benciloxicarbonilo y bencilcarbonilo, en particular seleccionado de acetilo, metoxicarbonilo y etoxicarbonilo; por ejemplo, el compuesto (35a) y (35b).

10 Según una sexta realización preferida, los aspectos según la invención, en particular los métodos y usos, se refieren a

(26) 4-(3-fluoro-4-metilbencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;

15 o su profármaco, en el que el grupo hidroxilo conectado al átomo de carbono en la 6ª posición del grupo β-D-glucopiranosilo está sustituido con un sustituyente seleccionado de (alquil C₁₋₃)carbonilo, (alquil C₁₋₆)oxicarbonilo, feniloxicarbonilo, benciloxicarbonilo y bencilcarbonilo, en particular seleccionado de acetilo, metoxicarbonilo y etoxicarbonilo; por ejemplo, el compuesto (46) y (70).

Según una séptima realización preferida, los aspectos según la invención, en particular los métodos y usos, se refieren a

(28) 4-(3-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;

20 o su profármaco, en el que el grupo hidroxilo conectado al átomo de carbono en la 6ª posición del grupo β-D-glucopiranosilo está sustituido con un sustituyente seleccionado de (alquil C₁₋₃)carbonilo, (alquil C₁₋₆)oxicarbonilo, feniloxicarbonilo, benciloxicarbonilo y bencilcarbonilo, en particular seleccionado de acetilo, metoxicarbonilo y etoxicarbonilo; por ejemplo, el compuesto (62) y (64).

25 Cuando esta invención se refiere a pacientes que requieren tratamiento o prevención, se refiere principalmente al tratamiento y la prevención en seres humanos,

pero la sustancia activa también puede utilizarse en conformidad en medicina veterinaria con mamíferos.

Dentro del alcance de la presente invención, la composición farmacéutica que comprende un derivado de pirazol-O-glucósido seleccionado del grupo de compuestos (1) a (29), o su profármaco, o su sal farmacéuticamente aceptable, se administra preferiblemente por vía oral. Son posibles otras formas de administración y se describen a continuación. Además del tratamiento y/o la profilaxis, la terapia mencionada a continuación según esta invención es preferiblemente una monoterapia, es decir, durante el transcurso de la terapia preferiblemente no se administra ningún otro fármaco antidiabético distinto del compuesto de esta invención al paciente.

Como se describió anteriormente, mediante la administración de un derivado de pirazol-O-glucósido según esta invención, o su profármaco o sal farmacéuticamente aceptable, se excreta el exceso de glucosa sanguínea a través de la orina del paciente, de forma que no se produce un aumento de peso e incluso puede reducirse el peso. Por tanto, un tratamiento o profilaxis según la invención es ventajosamente adecuado para aquellos pacientes que necesiten este tratamiento o profilaxis, que están diagnosticados con uno o más trastornos seleccionados del grupo que consiste en sobrepeso, obesidad de clase I, obesidad de clase II, obesidad de clase III, obesidad visceral y obesidad abdominal, o para aquellos individuos en los que está contraindicado un aumento de peso.

Se ha descubierto que un derivado de pirazol-O-glucósido según esta invención, o su profármaco o sal farmacéuticamente aceptable, muestra una eficacia muy buena con respecto al control glucémico, en particular en vista de una reducción de la glucosa plasmática en ayunas, la glucosa plasmática posprandial y/o la hemoglobina glicosilada (HbA1c). Mediante la administración de un derivado de pirazol-O-glucósido según esta invención, o su profármaco o sal farmacéuticamente aceptable, puede lograrse una reducción de HbA1c igual o mayor que preferiblemente 0,5 %, aún más preferiblemente igual o mayor que 1,0 %, y la reducción se encuentra, en particular, en el intervalo de 1,0 % a 1,5 %.

Además, el método según esta invención se aplica de forma ventajosa a aquellos pacientes que muestran uno, dos o más de los siguientes trastornos:

- (a) una concentración de glucosa sanguínea o de glucosa sérica en ayunas mayor que 110 mg/dl, en particular mayor que 125 mg/dl;
- (b) una concentración de glucosa plasmática posprandial igual o mayor que 140 mg/dl;

- (c) un valor de HbA1c igual o mayor que 6,5 %, en particular igual o mayor que 8,0 %.

La presente invención también describe el uso de una composición farmacéutica para mejorar el control glucémico en pacientes que tienen diabetes de tipo 2, o que muestran las primeras señales de prediabetes. Por tanto, la invención también incluye la prevención de la diabetes. Por tanto, si un derivado de pirazol-O-glucósido según esta invención, o su profármaco o sal farmacéuticamente aceptable, se utiliza inmediatamente para mejorar el control glucémico en cuanto una de las señales de prediabetes mencionadas anteriormente está presente, la aparición de una diabetes mellitus de tipo 2 manifiesta puede retrasarse o prevenirse.

Además, el derivado de pirazol-O-glucósido según esta invención, o su profármaco o sal farmacéuticamente aceptable, es particularmente adecuado en el tratamiento de pacientes con dependencia de la insulina, es decir, en pacientes que se tratan, o de otra manera serían tratados o necesitan tratamiento, con insulina o un derivado de insulina o un sustituto de la insulina o una formulación que comprende insulina o su derivado o sustituto. Estos pacientes incluyen pacientes con diabetes de tipo 2 y pacientes con diabetes de tipo 1.

Puede descubrirse que cuando se utiliza un derivado de pirazol-O-glucósido según esta invención, o su profármaco o sal farmacéuticamente aceptable, puede lograrse una mejora del control glucémico incluso en aquellos pacientes que tienen un control glucémico insuficiente, en particular a pesar de un tratamiento con uno o más fármacos antidiabéticos, por ejemplo, a pesar de una dosis máxima tolerada de una monoterapia oral con metformina o un antidiabético de la clase de las sulfonilureas. Una dosis máxima tolerada con respecto a la metformina es, por ejemplo, 850 mg tres veces diarias o cualquier equivalente a esto. En el alcance de la presente invención, la expresión "control glucémico insuficiente" significa un trastorno en el que los pacientes muestran unos valores de HbA1c mayores que 6,5 %, en particular mayores que 8 %.

Por tanto, según una realización preferida de la presente invención, se proporciona un método para mejorar el control glucémico y/o para reducir la glucosa plasmática en ayunas, la glucosa plasmática posprandial y/o la hemoglobina HbA1c glicosilada en un paciente que lo necesite, que está diagnosticado con una tolerancia alterada a la glucosa, con resistencia a la insulina, con el síndrome metabólico y/o con diabetes mellitus de tipo 1 o de tipo 2, que se caracteriza porque se administra una composición farmacéutica que comprende un derivado de pirazol-O-glucósido según esta invención, o su profármaco o sal farmacéuticamente aceptable.

Se ha descubierto que la disminución en el nivel de glucosa sanguínea mediante la administración de un derivado de pirazol-O-glucósido según esta invención, o su profármaco o sal farmacéuticamente aceptable, es independiente de insulina. Por tanto, un derivado de pirazol-O-glucósido según esta invención, o su profármaco o sal farmacéuticamente aceptable, es particularmente adecuado en el tratamiento de

- resistencia a la insulina,
- hiperinsulinemia,
- prediabetes,
- 10 - diabetes mellitus de tipo 2, en particular que tengan una etapa tardía de la diabetes mellitus de tipo 2,
- diabetes mellitus de tipo 1.

Además, un derivado de pirazol-O-glucósido según esta invención, o su profármaco o sal farmacéuticamente aceptable, es particularmente adecuado en el

- 15 tratamiento de pacientes diagnosticados con uno o más de los siguientes trastornos
- (a) obesidad (incluyendo obesidad de clase I, II y/o III), obesidad visceral y/u obesidad abdominal,
 - (b) nivel sanguíneo de triglicéridos ≥ 150 mg/dl,
 - (c) nivel sanguíneo de colesterol HDL < 40 mg/dl en pacientes femeninos, y < 50
 - 20 mg/dl en pacientes masculinos,
 - (d) una presión sanguínea sistólica ≥ 130 mm Hg, y una presión sanguínea diastólica ≥ 85 mm Hg,
 - (e) un nivel sanguíneo de glucosa en ayunas ≥ 110 mg/dl.

Se supone que los pacientes diagnosticados con una tolerancia alterada a la

25 glucosa, con resistencia a la insulina y/o con el síndrome metabólico sufren de un riesgo mayor de desarrollar una enfermedad cardiovascular como, por ejemplo, infarto de miocardio, enfermedad cardíaca coronaria, insuficiencia cardíaca, acontecimientos tromboembólicos. Un control glucémico según esta invención puede producir una reducción de los riesgos cardiovasculares.

30 Los derivados de pirazol-O-glucósido según esta invención, o sus profármacos o sales farmacéuticamente aceptables, muestran un buen perfil de seguridad. Por tanto, un tratamiento o profilaxis según esta invención es ventajosamente posible en aquellos pacientes para los cuales el tratamiento con otros fármacos antidiabéticos como, por ejemplo, metformina, está contraindicado y/o que presentan intolerancia

35 antes estos fármacos en dosis terapéuticas. En particular, un tratamiento o profilaxis

según esta invención es ventajosamente posible en aquellos pacientes que muestran o tienen un riesgo mayor de uno o más de los siguientes trastornos: insuficiencia o enfermedades renales, enfermedades cardíacas, insuficiencia cardíaca, enfermedades hepáticas, enfermedades pulmonares, estados catabólicos y/o peligro de acidosis de lactato, o pacientes femeninos que están embarazadas o durante la lactancia.

Además, puede descubrirse que la administración de un derivado de pirazol-O-glucósido según esta invención, o su profármaco o sal farmacéuticamente aceptable, no produce, o produce un riesgo bajo de hipoglucemia. Por tanto, un tratamiento o profilaxis según esta invención también es ventajosamente posible en aquellos pacientes que muestran o tienen un riesgo mayor de hipoglucemia.

Los derivados de pirazol-O-glucósido según esta invención, o sus profármacos o sales farmacéuticamente aceptables, son particularmente adecuados en el tratamiento o profilaxis a largo plazo de las enfermedades y/o trastornos descritos anterior y posteriormente en la presente, en particular en el control glucémico a largo plazo de pacientes con diabetes mellitus de tipo 2.

La expresión "a largo plazo" como se utiliza anterior y posteriormente, indica un tratamiento o la administración a un paciente dentro de un periodo de tiempo mayor que 12 semanas, preferiblemente mayor que 25 semanas, aún más preferiblemente mayor que un año.

Por tanto, una realización particularmente preferida de la presente invención proporciona un método para la terapia oral, preferiblemente la monoterapia oral, para la mejora, en especial la mejora a largo plazo del control glucémico en pacientes con diabetes mellitus de tipo 2, en especial en pacientes con una etapa tardía de la diabetes mellitus de tipo 2, en particular en pacientes que también están diagnosticados con sobrepeso, obesidad (incluyendo la obesidad de clase I, de clase II y/o de clase III), obesidad visceral y/u obesidad abdominal.

Se apreciará que la cantidad de derivado de pirazol-O-glucósido según esta invención, o su profármaco o sal farmacéuticamente aceptable, que se va a administrar al paciente y se requiere para su uso en el tratamiento o profilaxis según la presente invención variará según la vía de administración, la naturaleza y gravedad del trastorno para el cual se requiere el tratamiento o profilaxis, la edad, peso y trastorno del paciente, la medicación concomitante y, en último término, estará a discreción del médico encargado. Sin embargo, en general, el derivado de pirazol-O-glucósido según esta invención, o su profármaco o sal farmacéuticamente aceptable, se incluye en la

composición farmacéutica o forma de dosificación en una cantidad suficiente para mejorar el control glucémico en el paciente que se está tratando.

La composición farmacéutica que se va a administrar al paciente según un método descrito anterior y posteriormente en la presente comprende preferiblemente una cantidad en el intervalo de 1 mg a 1000 mg, aún más preferiblemente de 10 a 500 mg, lo más preferible de 50 a 500 mg diarios de un derivado de pirazol-O-glucósido según esta invención, o su profármaco o sal farmacéuticamente aceptable, con respecto a un paciente adulto. Las cantidades anteriormente especificadas se prefieren especialmente para la administración oral. Un ejemplo de una composición farmacéutica adecuada según esta invención es un comprimido para la administración oral que comprende 200 mg de 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol.

La dosis deseada de la composición farmacéutica según esta invención puede presentarse, de forma conveniente, en una dosis única una vez diaria, o como una dosis dividida administrada en intervalos apropiados, por ejemplo como dos, tres o más dosis diarias.

La composición farmacéutica puede formularse para la administración oral, rectal, nasal, tópica (incluyendo bucal y sublingual), transdérmica, vaginal o parenteral (incluyendo intramuscular, subcutánea e intravenosa) en una forma líquida o sólida, o en una forma adecuada para la administración mediante inhalación o insuflación. Cuando sea apropiado, las formulaciones pueden prepararse de modo conveniente en unidades de dosificación discretas, y pueden prepararse mediante cualquiera de los métodos bien conocidos en el técnica de la farmacia. Todos los métodos incluyen la etapa de poner en asociación el compuesto activo con vehículos líquidos, o vehículos sólidos finamente divididos, o ambos, y después, si es necesario, dar forma al producto para producir la formulación deseada.

La composición farmacéutica puede formularse en forma de comprimidos, gránulos, gránulos finos, polvos, cápsulas, comprimidos oblongos, cápsulas blandas, píldoras, disoluciones orales, jarabes, jarabes secos, comprimidos masticables, trociscos, comprimidos efervescentes, gotas, suspensiones, comprimidos de disolución rápida, comprimidos de dispersión rápida orales, etc.

La composición farmacéutica comprende preferiblemente uno o más vehículos farmacéuticos aceptables que deben ser "aceptables" en el sentido de ser compatibles con los otros ingredientes de la formulación y no ser perjudiciales para el receptor.

Las composiciones farmacéuticas adecuadas para la administración oral pueden presentarse de forma conveniente como unidades discretas como cápsulas, incluyendo cápsulas de gelatina blanca, sellos o comprimidos que contienen, cada uno, una cantidad predeterminada del ingrediente activo; como un polvo o gránulos; como una disolución, una suspensión o una emulsión, por ejemplo, como jarabes, elixires o sistemas de administración autoemulsionantes (SEDDS). El ingrediente activo también puede presentarse como una inyección en embolada, electuario o pasta. Los comprimidos y cápsulas para la administración oral pueden contener excipientes convencionales como agentes ligantes, cargas, lubricantes, disgregantes o agentes humectantes. Los comprimidos pueden estar revestidos según métodos muy conocidos en la técnica. Las preparaciones líquidas orales puede estar en forma, por ejemplo, de suspensiones, disoluciones, emulsiones, jarabes o elixires acuosos u oleosos, o pueden presentarse como un producto seco para su constitución con agua u otro vehículo adecuado antes del uso. Estas preparaciones líquidas pueden contener aditivos convencionales, como agentes suspensores, agentes emulsionantes, vehículos no acuosos (que pueden incluir aceites comestibles), o conservantes.

La composición farmacéutica según la invención también puede formularse para la administración parenteral (por ejemplo, mediante inyección, por ejemplo, inyección en embolada o infusión continua) y puede presentarse en una forma de dosificación unitaria en ampollas, jeringas prerrellenas, infusión de pequeño volumen y en recipientes de múltiples dosis con un conservante añadido. Las composiciones pueden tomar la forma de suspensiones, disoluciones o emulsiones en vehículos oleosos o acuosos, y pueden contener agentes de formulación, como agentes suspensores, estabilizantes y/o dispersantes. Como alternativa, el ingrediente activo puede estar en forma de polvo, obtenido mediante el aislamiento aseptico del sólido estéril, o mediante liofilización a partir de una disolución, para su constitución con un vehículo adecuado, por ejemplo, agua apirógena estéril, antes de su uso.

Las composiciones farmacéuticas adecuadas para la administración rectal, en las que el vehículo es un sólido, se presentan lo más preferiblemente como supositorios de dosis unitarias. Los vehículos adecuados incluyen mantequilla de cacao y otros materiales utilizados habitualmente en la técnica, y los supositorios pueden formarse, de modo conveniente, mediante la mezcla del(los) compuesto(s) activo(s) con un(os) vehículo(s) ablandado(s) o fundido(s), seguido de un enfriamiento e introducción en moldes para dar la forma.

Los ejemplos de vehículos farmacéuticamente aceptables son conocidos por los expertos en la técnica.

Los métodos para la fabricación de derivados de pirazol-O-glucósido según esta invención y sus profármacos son conocidos por los expertos en la técnica. De forma ventajosa, los compuestos según esta invención pueden prepararse utilizando métodos sintéticos como se describe en la bibliografía, en particular como se describe en los documentos EP 1338603 A1, EP 1389621 A1, WO 04/014932, WO 04/018491, WO 04/019958, WO 04/031203, WO 04/050122 y WO 03/020737. Los métodos preferidos para la síntesis de los compuestos según esta invención se describen en los ejemplos.

Cuando los compuestos según esta invención pueden formar sales, las sales deben ser farmacéuticamente aceptables. Las sales farmacéuticamente aceptables incluyen sales de ácidos inorgánicos, como ácido clorhídrico, ácido sulfúrico y ácido fosfórico; sales de ácidos carboxílicos orgánicos, como ácido oxálico, ácido acético, ácido cítrico, ácido málico, ácido benzoico, ácido maleico, ácido fumárico, ácido tartárico, ácido succínico y ácido glutámico, y sales de ácidos sulfónicos orgánicos, como ácido metansulfónico y ácido p-toluensulfónico. Las sales pueden formarse combinando los compuestos de esta invención y un ácido en la cantidad y proporción apropiadas en un disolvente y descomponer. También pueden obtenerse mediante un intercambio del catión o anión a partir de la forma de otras sales.

Los compuestos según esta invención incluyen solvatos, como hidratos y aductos alcohólicos.

Las propiedades biológicas de los nuevos compuestos pueden investigarse como se describe, por ejemplo, en el documento EP 1338603 A1, en particular con respecto a la actividad inhibidora sobre la recaptación de glucosa en la membrana de borde piloso renal, y a la actividad sobre la excreción de azúcar en la orina en ratas. Además, pueden aplicarse los siguientes ensayos:

La capacidad de las sustancias para inhibir la actividad SGLT-2 puede demostrarse en una estructura de ensayo en la que una línea celular CHO-K1 (ATCC nº CCL 61) o, como alternativa, una línea celular HEK293 (ATCC nº CRL-1573), que está transfectada de forma estable con un vector de expresión pZeoSV (Invitrogen, EMBL nº de registro L36849), que contiene el ADNc para la secuencia codificadora del cotransportador de glucosa y sodio humano 2 (Genbank nº de registro NM_003041) (CHO-hSGLT2 o HEK-hSGLT2). Estas líneas celulares transportan alfa-metil-

glucopiranosido marcado con ^{14}C (^{14}C -AMG, Amersham) hacia el interior de la célula de una manera dependiente de sodio.

El ensayo de SGLT-2 se realiza como sigue.

Células CHO-hSGLT2 se cultivan en medio F12 de Ham (BioWhittaker) con suero de ternera fetal al 10% y zeocina 250 $\mu\text{g/ml}$ (Invitrogen), y células HEK293-hSGLT2 se cultivan en medio DMEM con suero de ternera fetal al 10% y zeocina 250 $\mu\text{g/ml}$ (Invitrogen).

Las células se despegan de los matraces de cultivo lavando dos veces con PBS y posteriormente tratando con tripsina/EDTA. Después de la adición del medio de cultivo celular, las células se centrifugan, se resuspenden en medio de cultivo, y se cuentan en un contador de células Casy. Después se siembran 40.000 células por pocillo en una placa de 96 pocillos blanca revestida con poli-D-lisina y se incuban durante la noche a 37°C , CO_2 al 5%. Las células se lavan dos veces con 250 μl de tampón de ensayo (disolución salina equilibrada de Hanks, NaCl 137 mM, KCl 5,4 mM, CaCl_2 2,8 mM, MgSO_4 1,2 mM y HEPES 10 mM (pH 7,4), 50 $\mu\text{g/ml}$ de gentamicina). Entonces se añadieron 250 μl de tampón de ensayo y 5 μl de compuesto de ensayo a cada pocillo y la placa se incubó durante 15 minutos más en el incubador. Se utilizaron 5 μl de DMSO al 10% como control negativo. La reacción comienza añadiendo 5 μl de ^{14}C -AMG (0,05 μCi) a cada pocillo. Después de 2 horas de incubación a 37°C , CO_2 al 5%, las células se lavaron de nuevo con 250 μl de PBS (20°C) y después se lisaron mediante la adición de 25 μl de NaOH 0,1 N (5 min a 37°C). Se añadieron 200 μl de MicroScint20 (Packard) a cada pocillo y la incubación continúa durante 20 min más a 37°C . Después de esta incubación se mide la radiactividad del ^{14}C -AMG absorbida en un Topcount (Packard) utilizando un programa de centelleo de ^{14}C .

Para determinar la selectividad con respecto al SGLT1 humano se monta un ensayo análogo en el que se expresa el ADNc de hSGLT1 (Genbank nº de registro NM000343) en lugar del ADNc de hSGLT2 en las células CHO-K1 o HEK293.

En el texto anterior y siguiente, los átomos de H de los grupos hidroxilo no se muestran explícitamente en cada caso en las fórmulas estructurales. Los ejemplos que siguen pretenden ilustrar la presente invención sin restringirla.

Ejemplos

Anterior y posteriormente se utilizan las siguientes abreviaturas:

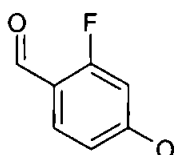
Bn	bencilo
Bu	butilo

	DCM	diclorometano
	DMF	dimetilformamida
	Et	etilo
	EtOAc	acetato de etilo
5	iPr	isopropilo
	i. vac.	al vacío
	Me	metilo
	Ph	fenilo
	TA	temperatura ambiente (aprox. 20°C)
10	THF	tetrahidrofurano

Preparación de los materiales de partida:

Ejemplo I

15 2-fluoro-4-hidroxibenzaldehído



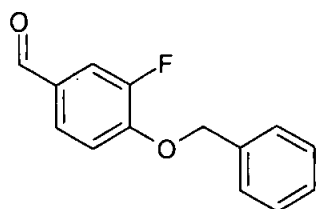
A una disolución a -70 °C de 2-fluoro-4-metoxibenzaldehído (19,1 g, 120 mmol) en CH₂Cl₂ (100 ml) se le añadió tribromuro de boro en CH₂Cl₂ (1 M, 160 ml, 160 mmol). Después de agitar la disolución de reacción a -68 °C durante 45 min se retiró el
20 baño de enfriamiento, y la disolución se volvió a agitar a temperatura ambiente durante la noche. La disolución de reacción se vertió en agua helada y se agitó durante 30 min. El precipitado formado se separó, se lavó con CH₂Cl₂, y se disolvió en EtOAc. La fase de EtOAc resultante se lavó con agua y se secó sobre MgSO₄. Después de la evaporación del disolvente, el residuo se lavó con un poco de CH₂Cl₂ y se secó al
25 vacío para producir el producto como un sólido de color beige.

Rendimiento: 14,5 g (86%).

ESI-EM: m/z = 139 [M-H]⁺

Ejemplo II

4-benciloxi-3-fluorobenzaldehído



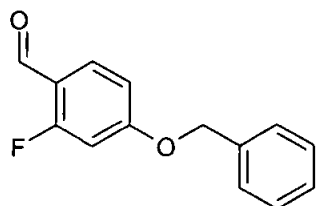
- 5 A una suspensión de 4-hidroxi-3-fluorobenzaldehído (10,0 g, 70 mmol) y carbonato de potasio (10,2 g, 74 mmol) en DMF (60 ml) se le añadió gota a gota bromuro de bencilo (8,7 ml, 74 mmol). La mezcla se agitó a temperatura ambiente durante 48 hora y posteriormente se extinguió con agua helada. La mezcla se volvió a diluir con agua y el precipitado se separó mediante filtración. El precipitado se lavó con agua y se disolvió en acetato de etilo. La disolución orgánica se lavó con salmuera, se secó sobre sulfato de sodio, y el disolvente se eliminó al vacío.

Rendimiento: 16,0 g (99%).

- 10 ESI-EM: $m/z = 231$ $[M+H]^+$

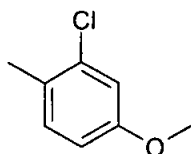
De una manera análoga pueden obtenerse los siguientes compuestos:

- (1) 4-benciloxi-2-fluorobenzaldehído



ESI-EM: $m/z = 253$ $[M+Na]^+$

- 15 (2) 2-cloro-4-metoxi-1-metilbenceno

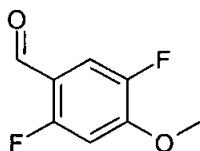


Se siguió el procedimiento anterior, excepto que se utilizó yoduro de metilo en lugar de bromuro de bencilo como electrófilo.

ESI-EM: $m/z = 156/158$ $[M]^+$ (cloro)

- 20 Ejemplo III

2,5-difluoro-4-metoxibenzaldehído



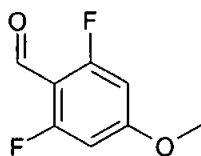
A una disolución a -65 °C de 1-bromo-2,5-difluoro-4-metoxibenceno (25,0 g, 0,11 mol) en THF (150 ml) y Et₂O (250 ml) bajo una atmósfera de Ar se le añadió gota a gota n-BuLi en hexano (1,6 M, 70 ml, 0,11 mol). Después de agitar la disolución a -65 °C durante 45 min, se añadió lentamente DMF (10 ml, 0,13 mol). La disolución se calentó en el baño de enfriamiento hasta alcanzar la temperatura ambiente durante la noche y después se diluyó con Et₂O (500 ml). La disolución orgánica resultante se lavó con salmuera, se secó sobre MgSO₄, y el disolvente se eliminó al vacío. El residuo se recrystalizó en iPr₂O para producir el producto como cristales amarillos.

Rendimiento: 6,7 g (35%).

10 R_f 0,63 (gel de sílice, éter de petróleo/EtOAc 1:1)

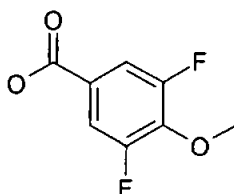
De una manera análoga pueden obtenerse los siguientes compuestos:

(1) 2,6-difluoro-4-metoxibenzaldehído



ESI-EM: m/z = 173 [M+H]⁺

15 (2) Ácido 3,5-difluoro-4-metoxibenzoico

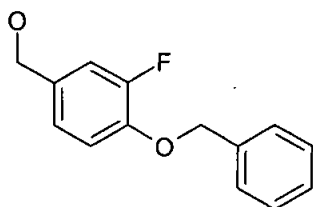


Se siguió el procedimiento anterior, excepto que la extinción del compuesto de aril-litio se realizó con hielo seco triturado (CO₂) en lugar de DMF.

ESI-EM: m/z = 187 [M-H]⁻

20 Ejemplo IV

(4-benciloxi-3-fluorofenil)metanol



A una suspensión de borohidruro de sodio (3,4 g, 90 mmol) en THF (60 ml) se le añadió una disolución de 4-benciloxi-3-fluorobenzaldehído (16,1 g, 70 mmol) en THF (60 ml). Después de agitar a temperatura ambiente durante la noche, la mezcla de

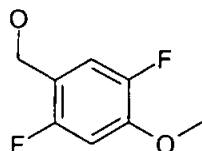
reacción se extinguió mediante la adición de agua helada. La mezcla se acidificó con HCl acuoso (4 M) y se extrajo con Et₂O. Las fases orgánicas reunidas se lavaron con una disolución acuosa de NaHCO₃ y se secaron sobre sulfato de sodio. Después de la eliminación del disolvente se obtuvo el producto.

5 Rendimiento: 16,2 g (100%).

ESI-EM: $m/z = 215$ [M-OH]⁺

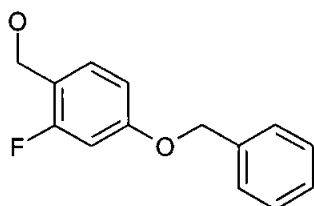
De una manera análoga pueden prepararse los siguientes compuestos:

(1) (2,5-difluoro-4-metoxifenil)metanol



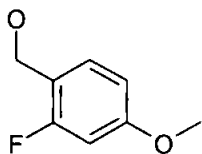
10 ESI-EM: $m/z = 215$ [M-OH]⁺

(2) (4-benciloxi-2-fluorofenil)metanol



ESI-EM: $m/z = 232$ [M]⁺

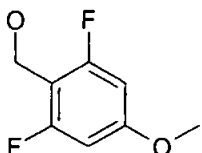
(3) (2-fluoro-4-metoxifenil)metanol



15

ESI-EM: $m/z = 139$ [M-OH]⁺

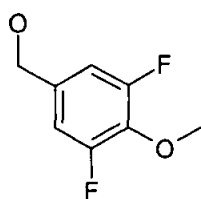
(4) (2,6-difluoro-4-metoxifenil)metanol



ESI-EM: $m/z = 157$ [M-OH+H]⁺

20 Ejemplo V

(3,5-difluoro-4-metoxifenil)metanol



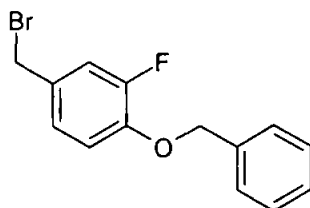
- 5 A una suspensión a 20 °C de hidruro de litio y aluminio (0,57 g, 15 mmol) en THF (50 ml) y tolueno (30 ml) se le añadió una disolución de ácido 3,5-difluoro-4-metoxibenzoico (2,9 g, 15 mmol) en THF (20 ml). Después de agitar la mezcla de reacción a temperatura ambiente durante la noche se añadió agua helada y la disolución resultante se acidificó con ácido sulfúrico 2 N. La capa orgánica se separó y la capa acuosa se extrajo con EtOAc. Las fases orgánicas reunidas se lavaron con una disolución acuosa de NaHCO₃ y salmuera, y se secaron sobre MgSO₄. Después de la eliminación del disolvente, el residuo se purificó mediante una cromatografía en gel de sílice (éter de petróleo/EtOAc 2:1).
- 10

Rendimiento: 1,6 g (60%).

R_f 0,7 (gel de sílice, éter de petróleo/EtOAc 1:1)

Ejemplo VI

1-benciloxi-4-bromometil-2-fluorobenceno

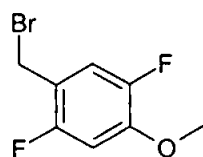


15

- A una disolución enfriada en hielo de (4-benciloxi-3-fluorofenil)metanol (16,7 g, 72 mmol) en éter dietílico (130 ml) se le añadió tribromuro de fósforo (2,8 ml, 30 mmol) a una velocidad tal que la temperatura de la disolución no aumentó por encima de 8 °C. Después de agitar a temperatura ambiente durante 2 h, la mezcla de reacción se enfrió en un baño de hielo y se extinguió mediante la adición de agua helada, acetato de etilo y Et₂O. La capa orgánica se separó, y se lavó con una disolución acuosa de NaHCO₃ y salmuera. Después de la evaporación del disolvente se obtuvo el producto.
- 20
- Rendimiento: 20,5 g (97%).

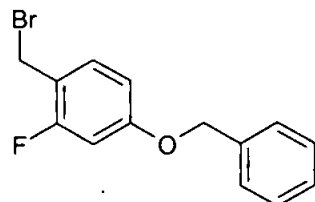
ESI-EM: m/z = 294/296 [M]⁺ (bromo)

- 25 De una manera análoga se prepararon los siguientes compuestos:
- (1) 1-bromometil-2,5-difluoro-4-metoxibenceno



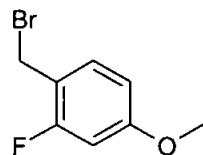
ESI-EM: $m/z = 236/238$ $[M]^+$ (bromo)

(2) 4-benzyloxy-1-bromometil-2-fluorobenceno



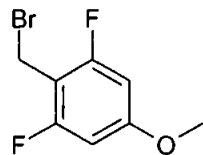
5 ESI-EM: $m/z = 294/296$ $[M]^+$ (bromo)

(3) 1-bromometil-2-fluoro-4-metoxibenceno



R_f 0,8 (gel de sílice, éter de petróleo/EtOAc 1:1)

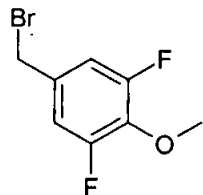
(4) 2-bromometil-1,3-difluoro-5-metoxibenceno



10

ESI-EM: $m/z = 236/238$ $[M]^+$ (bromo)

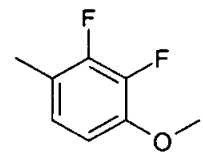
(5) 5-bromometil-1,3-difluoro-2-metoxibenceno



ESI-EM: $m/z = 236/238$ $[M]^+$ (bromo)

15 Ejemplo VII

2,3-difluoro-1-metoxi-4-metilbenceno



- 37 -

A una disolución a 20 °C de hidróxido de sodio (14,4 g, 0,36 mol) y 2,3-difluoro-4-metilfenol (50,0 g, 0,35 mol) en agua (160 ml) se le añadió gota a gota sulfato de dimetilo (34 ml, 0,36 mol). Después de agitar a temperatura ambiente durante la noche, la disolución de reacción se extrajo con Et₂O. La fase etérea se lavó con una

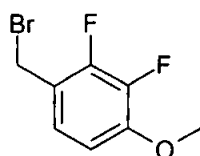
5 disolución de NaOH 2 N, agua y salmuera, y posteriormente se secó sobre MgSO₄. Después de la eliminación del disolvente a presión reducida se obtuvo el producto como un aceite incoloro.

Rendimiento: 49,0 g (89%).

ESI-EM: m/z = 158 [M]⁺

10 Ejemplo VIII

1-bromometil-2,3-difluoro-4-metoxibenceno



Una disolución de 2,3-difluoro-1-metoxi-4-metilbenceno (39,5 g, 0,25 mol), N-bromosuccinimida (44,5 g, 0,25 mol) y azobisisobutironitrilo (0,41 g, 2,5 mmol) en CCl₄

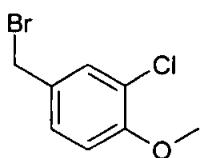
15 (300 ml) se agitó a reflujo durante 3,5 h. Después la succinimida formada se retiró mediante filtración, y el filtrado se concentró al vacío. El residuo se disolvió en Et₂O (200 ml) y se concentró hasta aproximadamente 100 ml. Después de enfriar en un baño de hielo el precipitado formado se retiró mediante filtración, se lavó con Et₂O frío, y se secó al vacío para producir el producto como un sólido blanco.

20 Rendimiento: 36,0 g (61%).

R_f 0,3 (gel de sílice, éter de petróleo/EtOAc 20:1)

Los siguientes compuestos pueden obtenerse por analogía con el procedimiento descrito anteriormente:

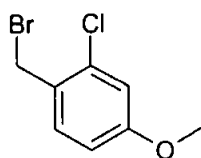
(1) 4-bromometil-2-cloro-1-metoxibenceno



25

R_f 0,4 (gel de sílice, éter de petróleo/EtOAc 20:1)

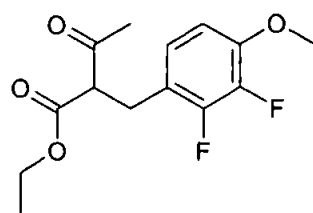
(2) 1-bromometil-2-cloro-4-metoxibenceno



R_f 0,5 (gel de sílice, éter de petróleo/EtOAc 20:1)

Ejemplo IX

Éster etílico del ácido 2-(2,3-difluoro-4-metoxibencil)-3-oxobutírico



5

A una suspensión enfriada en hielo de hidruro de sodio (4,8 g, 120 mmol, al 60% en aceite mineral, exento de aceite con pentano) en THF (140 ml) se le añadió el éster etílico del ácido 3-oxobutírico (17,2 g, 132 mmol) en THF (50 ml). Después de retirar el baño de hielo y de agitar la disolución a temperatura ambiente durante 0,5 h,

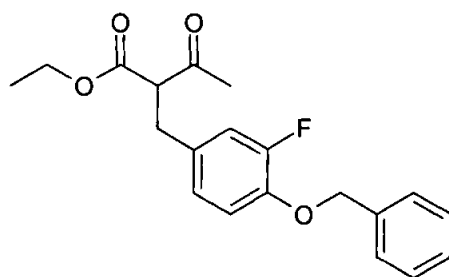
10 se añadió gota a gota una disolución de 1-metoxi-4-bromometil-2,3-difluorobenceno (28,4 g, 120 mmol) en THF (60 ml). Después de agitar la mezcla de reacción a reflujo durante la noche, el disolvente se eliminó al vacío y el residuo se trituroó con Et₂O (300 ml). La fase etérea se lavó con agua y salmuera y se secó sobre MgSO₄. Se obtuvo el producto como un aceite amarillo después de la evaporación del disolvente.

15 Rendimiento: 35,5 g (con una pureza de aprox. 80%).

ESI-EM: m/z = 285 [M-H]⁻

De una manera análoga pueden obtenerse los siguientes compuestos:

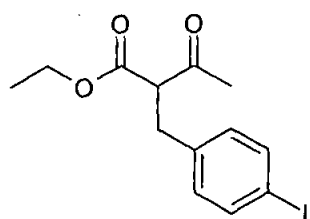
(1) Éster etílico del ácido 2-(4-benciloxi-3-fluorobencil)-3-oxobutírico



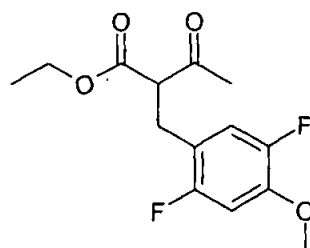
20 ESI-EM: m/z = 345 [M+H]⁺

(2) Éster etílico del ácido 2-(4-yodobencil)-3-oxobutírico

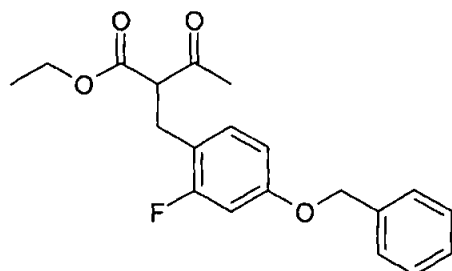
- 39 -

ESI-EM: $m/z = 345$ $[M-H]^+$

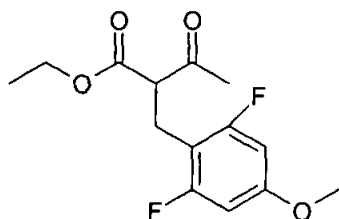
(3) Éster etílico del ácido 2-(2,5-difluoro-4-metoxibencil)-3-oxobutírico

5 R_f 0,27 (gel de sílice, éter de petróleo/EtOAc 4:1)

(4) Éster etílico del ácido 2-(4-benciloxi-2-fluorobencil)-3-oxobutírico

ESI-EM: $m/z = 343$ $[M-H]^+$

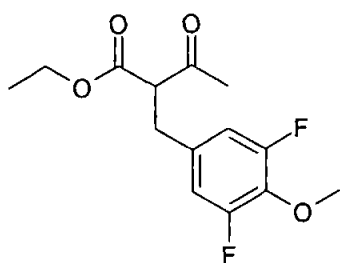
(5) Éster etílico del ácido 2-(2,6-difluoro-4-metoxibencil)-3-oxobutírico



10

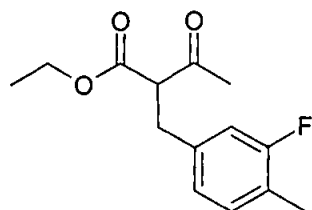
ESI-EM: $m/z = 287$ $[M+H]^+$

(6) Éster etílico del ácido 2-(3,5-difluoro-4-metoxibencil)-3-oxobutírico



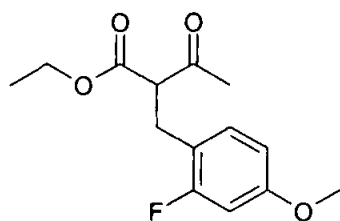
ESI-EM: $m/z = 287 [M+H]^+$

(7) Éster etílico del ácido 2-(3-fluoro-4-metilbencil)-3-oxobutírico



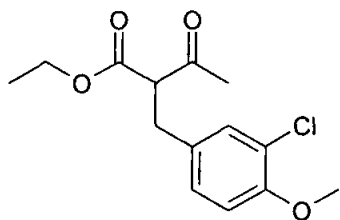
5 ESI-EM: $m/z = 253 [M+H]^+$

(8) Éster etílico del ácido 2-(2-fluoro-4-metoxibencil)-3-oxobutírico



ESI-EM: $m/z = 269 [M+H]^+$

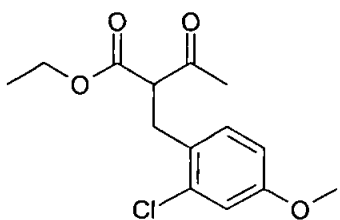
(9) Éster etílico del ácido 2-(3-cloro-4-metoxibencil)-3-oxobutírico



10

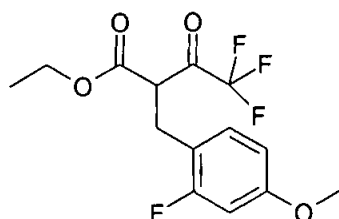
ESI-EM: $m/z = 283/285 [M-H]^-$ (cloro)

(10) Éster etílico del ácido 2-(2-cloro-4-metoxibencil)-3-oxobutírico



ESI-EM: $m/z = 285/287 [M+H]^+$ (cloro)

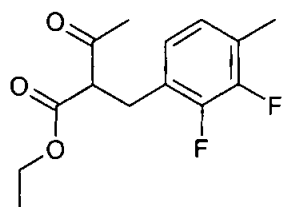
(11) Éster etílico del ácido 4,4,4-trifluoro-2-(2-fluoro-4-metoxibencil)-3-oxobutírico



ESI-EM: $m/z = 321$ $[M-H]^+$

Ejemplo X

5 Éster etílico del ácido 2-(2,3-difluoro-4-metilbencil)-3-oxobutírico



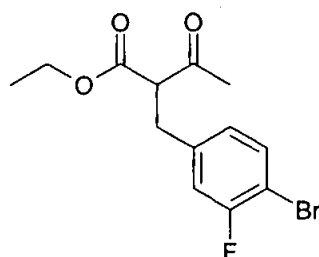
A una disolución enfriada en hielo del éster etílico del ácido 3-oxobutírico (4,17 g, 32,1 mmol) y yoduro de sodio (23,9 g, 160 mmol) bajo una atmósfera de Ar en acetonitrilo (220 ml) se le añadió a lo largo de 3 min cloruro de trimetilsililo (20,2 ml, 160 mmol), seguido de 2,3-difluoro-4-metilbenzaldehído (5,0 g, 32,1 mmol). Se retiró el baño de hielo, y la mezcla de reacción se agitó a temperatura ambiente durante 8 h y posteriormente a 60 °C durante 15 h. Después de enfriar hasta la temperatura ambiente, la mezcla de reacción se vertió en una mezcla de EtOAc (300 ml) y agua (200 ml). La fase orgánica se separó y se lavó con una disolución acuosa de $Na_2S_2O_3$ y salmuera, y se secó sobre Na_2SO_4 . El disolvente se eliminó a presión reducida, y el residuo se purificó mediante una cromatografía en gel de sílice (hexano/EtOAc, 1:6) para producir el producto como un aceite incoloro.

Rendimiento: 8,4 g (97%).

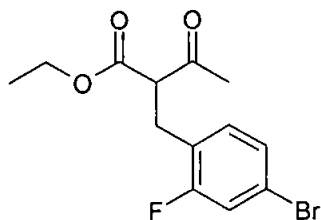
R_f 0,35 (gel de sílice, hexano/EtOAc 5:1)

20 De una manera análoga pueden obtenerse los siguientes compuestos:

(1) Éster etílico del ácido 2-(4-bromo-3-fluorobencil)-3-oxobutírico

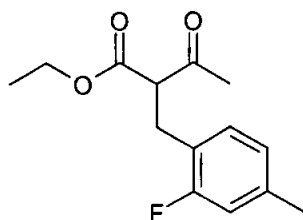


(2) Éster etílico del ácido 2-(4-bromo-2-fluorobencil)-3-oxobutírico



R_f 0,42 (gel de sílice, hexano/EtOAc 4:1)

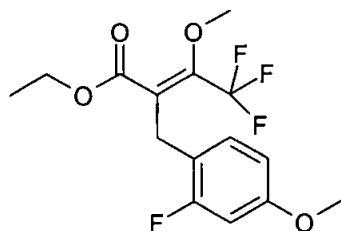
(3) Éster etílico del ácido 2-(2-fluoro-4-metilbencil)-3-oxobutírico



5

Ejemplo XI

Éster etílico del ácido 4,4,4-trifluoro-2-(2-fluoro-4-metoxibencil)-3-metoxibut-2-enoico



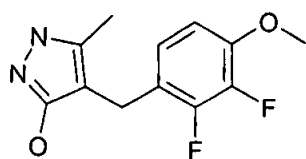
A una mezcla a 20 °C del éster etílico del ácido 4,4,4-trifluoro-2-(2-fluoro-4-metoxibencil)-3-oxobutírico (6,35 g, 19,7 mmol) y carbonato de cesio (9,5 g, 28,9 mmol) en DMF (50 ml) se le añadió gota a gota una disolución del éster metílico del ácido toluen-4-sulfónico (4,5 g, 23,7 mmol) en DMF (20 ml). La mezcla de reacción se agitó a temperatura ambiente durante la noche y posteriormente a 60 °C durante 1,5 h. Después de enfriar hasta la temperatura ambiente se añadió ácido fosfórico diluido, y la disolución resultante se extrajo con Et₂O. Las fases orgánicas reunidas se lavaron con salmuera y se secaron sobre Na₂SO₄. Después de la eliminación del disolvente, el residuo se purificó mediante cromatografía en óxido de aluminio (ciclohexano/EtOAc 99:1->70:30).

Rendimiento: 6,6 g (100%).

ESI-EM: $m/z = 337 [M+H]^+$

Ejemplo XII

4-(2,3-difluoro-4-metoxibencil)-5-metil-1H-pirazol-3-ol



Una disolución del éster etílico del ácido 2-(2,3-difluoro-4-metoxibencil)-3-oxobutírico (33,0 g, 0,115 mol) e hidrato de hidrazina (al 80%, 8,0 g, 128 mmol) en EtOH (300 ml) se agitó a reflujo durante 2 h. Después de enfriar en un baño de hielo se recogió el precipitado, se lavó con EtOH frío, y se secó al vacío para producir el

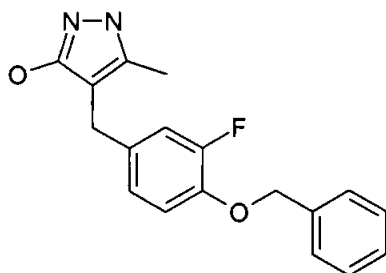
5 se recogió el precipitado, se lavó con EtOH frío, y se secó al vacío para producir el producto como un sólido blanco.

Rendimiento: 22,5 g (70%).

ESI-EM: $m/z = 255 [M+H]^+$

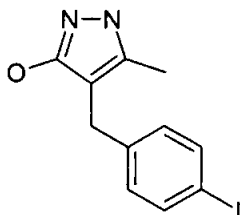
Los siguientes compuestos pueden obtenerse de una forma similar:

10 (1) 4-(4-benciloxi-3-fluorobencil)-5-metil-1H-pirazol-3-ol



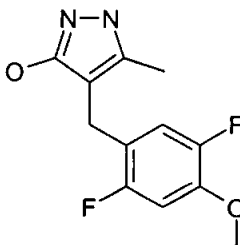
ESI-EM: $m/z = 313 [M+H]^+$

(2) 4-(4-yodobencil)-5-metil-1H-pirazol-3-ol



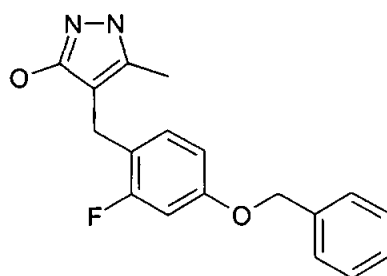
15 ESI-EM: $m/z = 315 [M+H]^+$

(3) 4-(2,5-difluoro-4-metoxibencil)-5-metil-1H-pirazol-3-ol



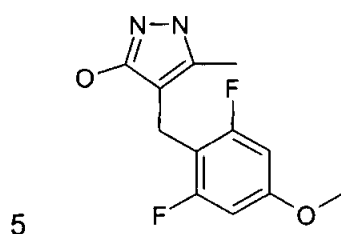
ESI-EM: $m/z = 255 [M+H]^+$

(4) 4-(4-benciloxi-2-fluorobencil)-5-metil-1H-pirazol-3-ol



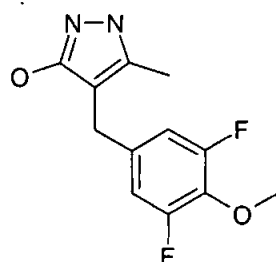
ESI-EM: $m/z = 313$ $[M+H]^+$

(5) 4-(2,6-difluoro-4-metoxibencil)-5-metil-1H-pirazol-3-ol



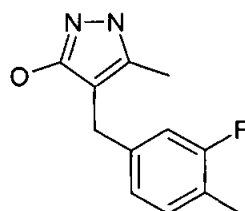
ESI-EM: $m/z = 255$ $[M+H]^+$

(6) 4-(3,5-difluoro-4-metoxibencil)-5-metil-1H-pirazol-3-ol



ESI-EM: $m/z = 255$ $[M+H]^+$

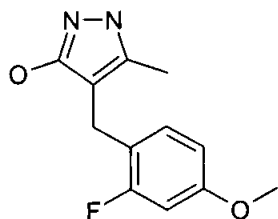
10 (7) 4-(3-fluoro-4-metilbencil)-5-metil-1H-pirazol-3-ol



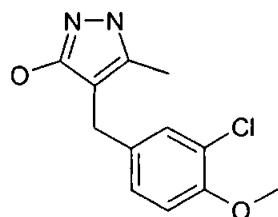
ESI-EM: $m/z = 221$ $[M+H]^+$

(8) 4-(2-fluoro-4-metoxibencil)-5-metil-1H-pirazol-3-ol

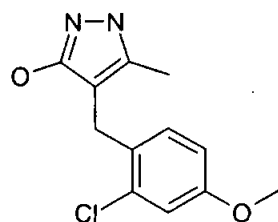
- 45 -

ESI-EM: $m/z = 237$ $[M+H]^+$

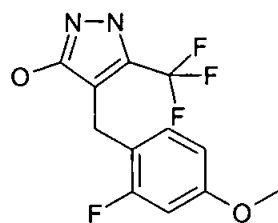
(9) 4-(3-cloro-4-metoxibencil)-5-metil-1H-pirazol-3-ol

5 ESI-EM: $m/z = 253/255$ $[M+H]^+$ (cloro)

(10) 4-(2-cloro-4-metoxibencil)-5-metil-1H-pirazol-3-ol

ESI-EM: $m/z = 253/255$ $[M+H]^+$ (cloro)

(11) 4-(2-fluoro-4-metoxibencil)-5-trifluorometil-1H-pirazol-3-ol

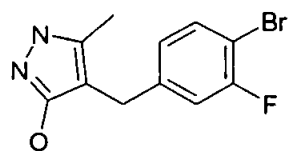


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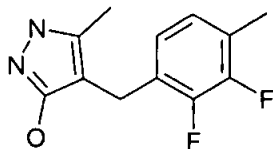
El producto se preparó siguiendo el procedimiento anterior, comenzando a partir del éster etílico del ácido 4,4,4-trifluoro-2-(2-fluoro-4-metoxibencil)-3-metoxibut-2-enoico

ESI-EM: $m/z = 289$ $[M-H]^-$

15 (12) 4-(4-bromo-3-fluorobencil)-5-metil-1H-pirazol-3-ol

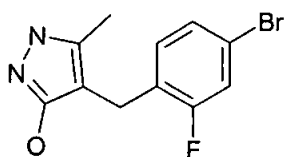


(13) 4-(2,3-difluoro-4-metilbencil)-5-metil-1H-pirazol-3-ol



R_f 0,05 (gel de sílice, hexano/EtOAc 5:1)

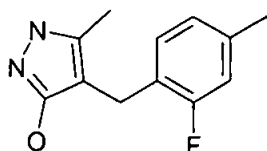
(14) 4-(4-bromo-2-fluorobencil)-5-metil-1H-pirazol-3-ol



5

R_f 0,15 (gel de sílice, hexano/EtOAc 1:1)

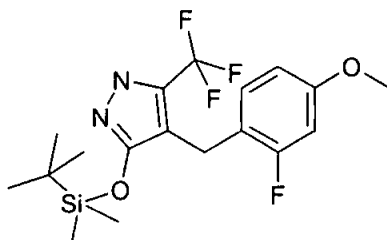
(15) 4-(2-fluoro-4-metilbencil)-5-metil-1H-pirazol-3-ol



R_f 0,11 (gel de sílice, hexano/EtOAc 1:1)

10 Ejemplo XIII

3-(terc-butildimetilsililo)-4-(2-fluoro-4-metoxibencil)-5-trifluorometil-1H-pirazol



15 A una disolución de 4-(2-fluoro-4-metoxibencil)-5-trifluorometil-1H-pirazol-3-ol (0,21 g, 0,72 mmol) e imidazol (8,0 g, 128 mmol) en DMF (2 ml) se le añadió cloruro de terc-butildimetilsililo (0,13 g, 0,86 mmol). Después de agitar a temperatura ambiente durante 4 h, la disolución se diluyó con EtOAc y se lavó con agua y salmuera. La fase orgánica se secó y el disolvente se eliminó.

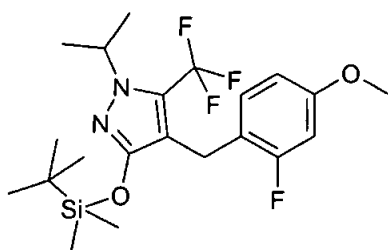
Rendimiento: 0,34 g (con una pureza de aprox. 80%).

ESI-EM: m/z = 405 [M+H]⁺

20 Ejemplo XIV

3-(terc-butildimetilsililo)-4-(2-fluoro-4-metoxibencil)-1-isopropil-5-trifluorometil-1H-pirazol

- 47 -



A una suspensión de 3-(terc-butildimetilsililoxi)-4-(2-fluoro-4-metoxibencil)-5-trifluorometil-1H-pirazol (0,27 g, 0,67 mmol) y Ph_3P (0,20 g, 0,76 mmol) en isopropanol (2 ml) se le añadió azodicarboxilato de dietilo en tolueno (al 40%, 0,35 ml, 0,76 mmol).

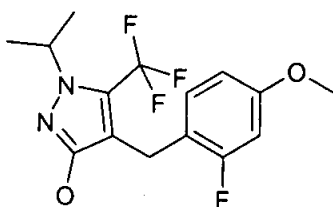
- 5 La disolución se agitó durante 1 h a temperatura ambiente y luego se diluyó con Et_2O . La disolución resultante se lavó con agua y una disolución acuosa de NaOH (2 N), se secó sobre Na_2SO_4 , y el disolvente se eliminó. El residuo se purificó mediante una cromatografía en gel de sílice (ciclohexano/ EtOAc 99:1-→4:1) para producir el producto como un aceite incoloro.

- 10 Rendimiento: 0,14 g (47%).

ESI-EM: $m/z = 447$ $[\text{M}+\text{H}]^+$

Ejemplo XV

4-(2-fluoro-4-metoxibencil)-1-isopropil-5-trifluorometil-1H-pirazol-3-ol



- 15 Una disolución de 3-(terc-butildimetilsililoxi)-4-(2-fluoro-4-metoxibencil)-1-isopropil-5-trifluorometil-1H-pirazol (0,27 g, 0,67 mmol), HCl acuoso (1 N, 1 ml, 1 mmol), MeOH (0,5 ml) y THF (12 ml) se agitó a 60 °C durante 2 h. Después de enfriar hasta la temperatura ambiente, la disolución se diluyó con EtOAc y se lavó con agua y salmuera. Se obtuvo el producto como un sólido blanco después de secar sobre

- 20 Na_2SO_4 y de la eliminación del disolvente al vacío.

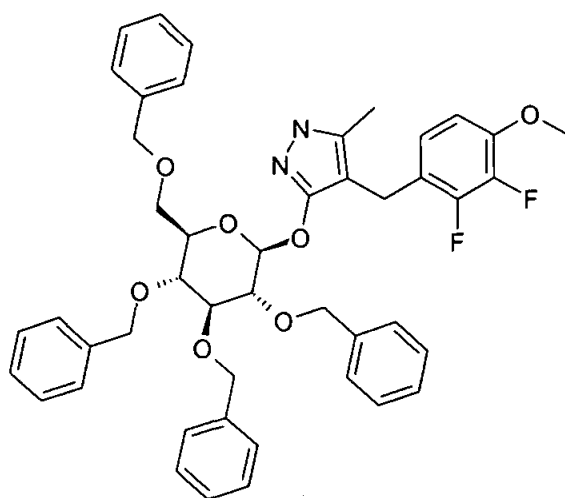
Rendimiento: 0,10 g (100%).

ESI-EM: $m/z = 333$ $[\text{M}+\text{H}]^+$

Ejemplo XVI

4-(2,3-difluoro-4-metoxibencil)-5-metil-3-(2,3,4,6-tetra-O-bencil-β-D-glucopiranos-1-

- 25 iloxi)-1H-pirazol

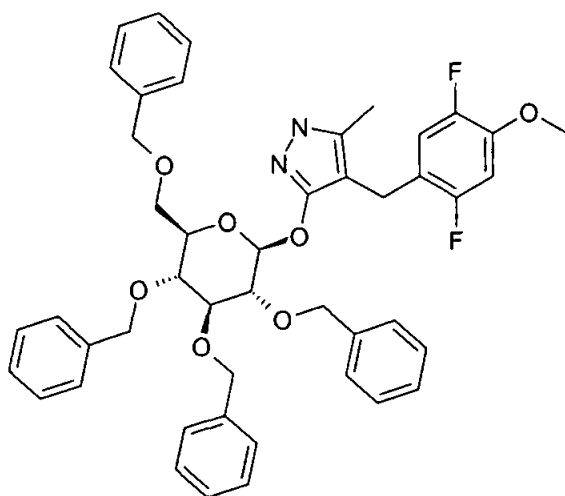


- A una disolución a 0 °C de 4-(2,3-difluoro-4-metoxibencil)-5-metil-1H-pirazol-3-ol (2,14 g, 8,4 mmol), 2,3,4,6-tetra-O-bencil- α -D-glucopiranososa (4,54 g, 8,4 mmol) y PPh_3 (2,20 g, 8,4 mmol) en THF seco (80 ml) se le añadió azodicarboxilato de dietilo en tolueno (al 40%, 3,85 ml, 8,4 mmol) a una velocidad tal que la disolución se mantuvo a 2-6 °C. Después de 10 min se retiró el baño de enfriamiento y la disolución de reacción se agitó a temperatura ambiente durante la noche. Después la disolución se concentró a 40 °C a presión reducida, y el resto se trató con Et_2O (50 ml). La disolución etérea se enfrió hasta -18 °C, y el precipitado en formación se separó y se lavó con Et_2O frío. El filtrado se diluyó con Et_2O y se lavó con una disolución acuosa de NaOH (2 N), agua y salmuera. Después de secar sobre MgSO_4 y de la evaporación del disolvente, el residuo se purificó mediante una cromatografía en gel de sílice (ciclohexano/ EtOAc 2:1- $\rightarrow$ 1:6). El producto purificado se recrystalizó en $i\text{Pr}_2\text{O}$ para producir el producto como un sólido blanco (<5% del anómero α).
- Rendimiento: 3,10 g (48%).
- ESI-EM: $m/z = 777$ $[\text{M}+\text{H}]^+$

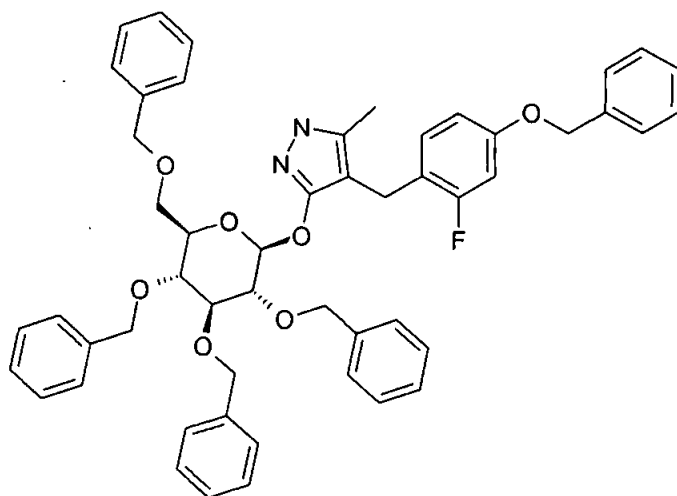
Los siguientes compuestos pueden obtenerse de una forma similar:

- (1) 4-(2,5-difluoro-4-metoxibencil)-5-metil-3-(2,3,4,6-tetra-O-bencil- β -D-glucopiranos-1-iloxi)-1H-pirazol

- 49 -

ESI-EM: $m/z = 777 [M+H]^+$

(2) 4-(2-fluoro-4-benzyloxybenzyl)-5-metil-3-(2,3,4,6-tetra-O-bencil-β-D-glucopiranos-1-iloxi)-1H-pirazol

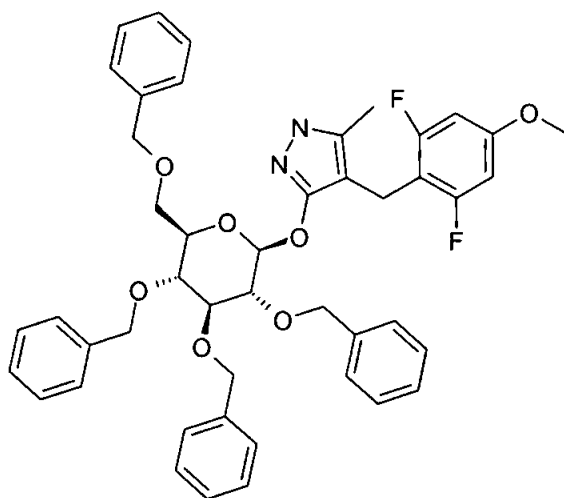


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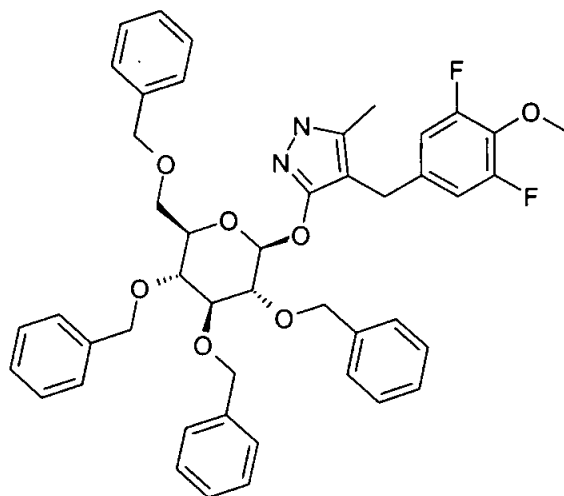
ESI-EM: $m/z = 835 [M+H]^+$

(3) 4-(2,6-difluoro-4-metoxibencil)-5-metil-3-(2,3,4,6-tetra-O-bencil-β-D-glucopiranos-1-iloxi)-1H-pirazol

- 50 -

ESI-EM: $m/z = 777$ $[M+H]^+$

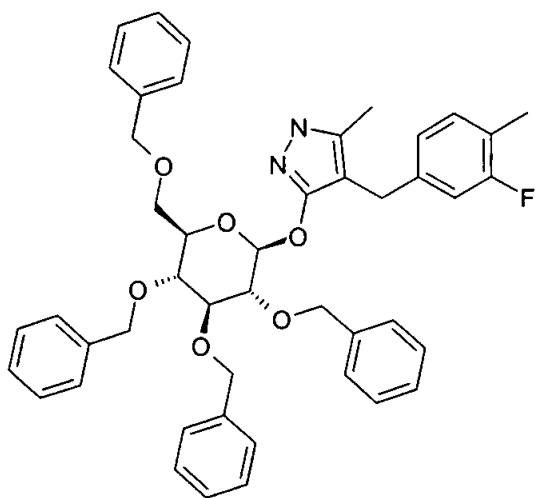
(4) 4-(3,5-difluoro-4-metoxibencil)-5-metil-3-(2,3,4,6-tetra-O-bencil-β-D-glucopiranos-1-iloxi)-1H-pirazol



5

ESI-EM: $m/z = 777$ $[M+H]^+$

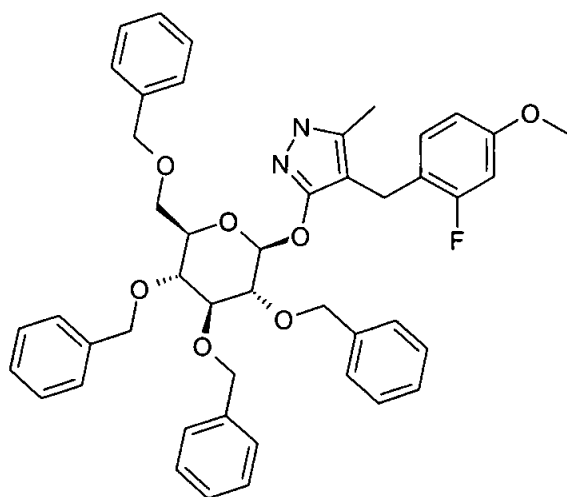
(5) 4-(3-fluoro-4-metilbencil)-5-metil-3-(2,3,4,6-tetra-O-bencil-β-D-glucopiranos-1-iloxi)-1H-pirazol



Se utilizaron Bu_3P y 1,1'-(azodicarbonil)dipiperidina en lugar de Ph_3P y azodicarboxilato de dietilo.

ESI-EM: $m/z = 743 [\text{M}+\text{H}]^+$

- 5 (6) 4-(2-fluoro-4-metoxibencil)-5-metil-3-(2,3,4,6-tetra-O-bencil-β-D-glucopiranos-1-iloxi)-1H-pirazol

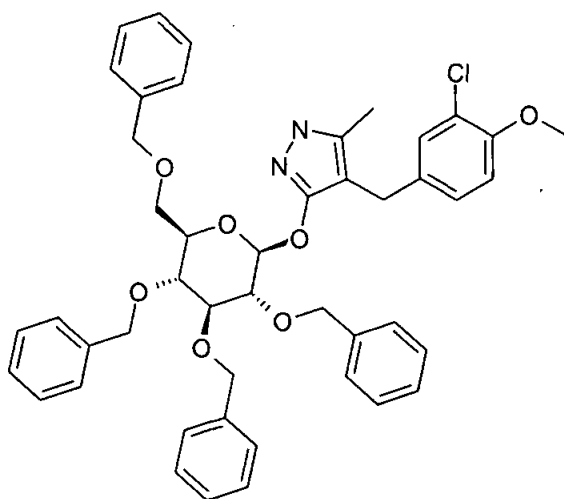


Se utilizaron Bu_3P y 1,1'-(azodicarbonil)dipiperidina en lugar de Ph_3P y azodicarboxilato de dietilo.

- 10 ESI-EM: $m/z = 759 [\text{M}+\text{H}]^+$

- (7) 4-(3-cloro-4-metoxibencil)-5-metil-3-(2,3,4,6-tetra-O-bencil-β-D-glucopiranos-1-iloxi)-1H-pirazol

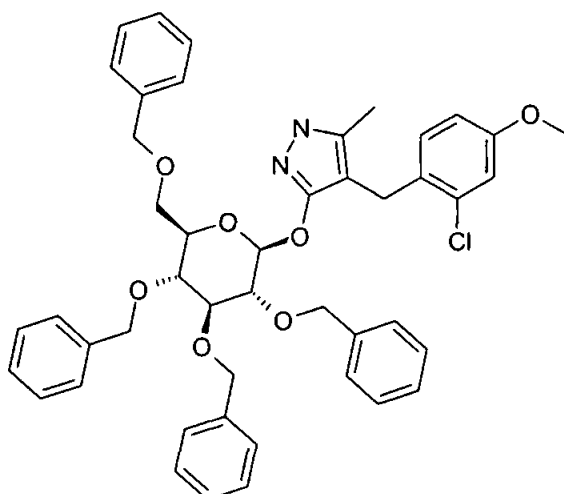
- 52 -



Se utilizaron Bu_3P y 1,1'-(azodicarbonil)dipiperidina en lugar de Ph_3P y azodicarboxilato de dietilo.

ESI-EM: $m/z = 775/777$ $[\text{M}+\text{H}]^+$ (cloro)

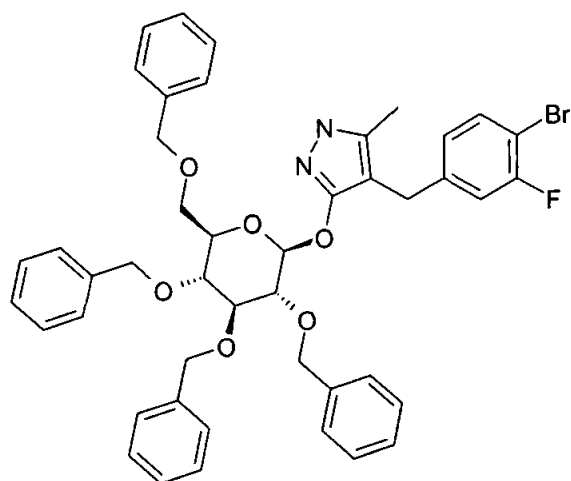
- 5 (8) 4-(2-cloro-4-metoxibencil)-5-metil-3-(2,3,4,6-tetra-O-bencil- β -D-glucopiranos-1-iloxi)-1H-pirazol



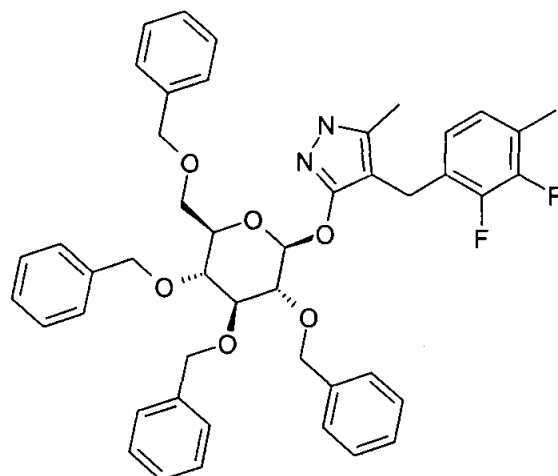
Se utilizaron Bu_3P y 1,1'-(azodicarbonil)dipiperidina en lugar de Ph_3P y azodicarboxilato de dietilo.

- 10 ESI-EM: $m/z = 775/777$ $[\text{M}+\text{H}]^+$ (cloro)

- (9) 4-(4-bromo-3-fluorobencil)-5-metil-3-(2,3,4,6-tetra-O-bencil- β -D-glucopiranos-1-iloxi)-1H-pirazol

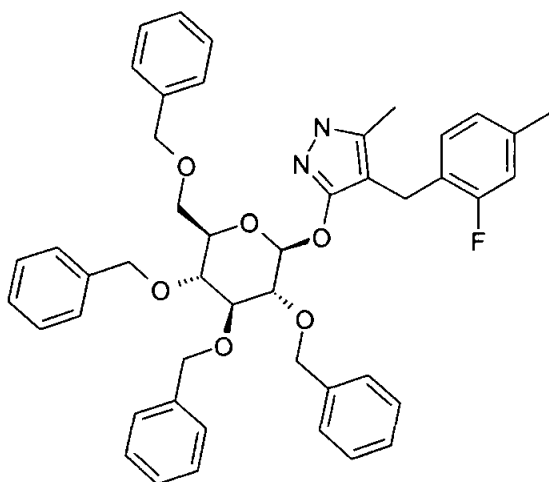


(10) 4-(2,3-difluoro-4-metilbencil)-5-metil-3-(2,3,4,6-tetra-O-bencil-β-D-glucopiranos-1-iloxi)-1H-pirazol



5 R_f 0,24 (gel de sílice, hexano/EtOAc 1:1)

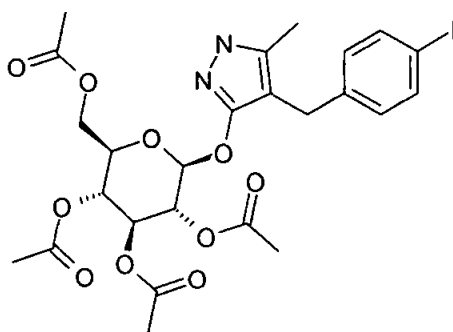
(11) 4-(2-fluoro-4-metilbencil)-5-metil-3-(2,3,4,6-tetra-O-bencil-β-D-glucopiranos-1-iloxi)-1H-pirazol



R_f 0,48 (gel de sílice, hexano/EtOAc 1:1)

Ejemplo XVII

4-(4-yodobencil)-5-metil-3-(2,3,4,6-tetra-O-acetil-β-D-glucopiranos-1-iloxi)-1H-pirazol



5

A una disolución de 4-(4-yodobencil)-5-metil-1H-pirazol-3-ol (0,70 g, 2,23 mmol) en THF seco (80 ml) se le añadió Ag₂CO₃ (0,65 g, 2,36 mmol), seguido de bromuro de 2,3,4,6-tetra-O-acetil-β-D-glucopiranos-1-ilo (1,00 g, 2,43 mmol). La mezcla de reacción se agitó a reflujo en la oscuridad durante la noche antes de la adición de otra porción de Ag₂CO₃ (0,75 g, 2,72 mmol) y bromuro de 2,3,4,6-tetra-O-acetil-β-D-glucopiranos-1-ilo (1,10 g, 2,68 mmol). La mezcla de reacción se agitó a reflujo durante otra noche y después se enfrió hasta la temperatura ambiente. La mezcla se filtró, y el filtrado se concentró al vacío. El residuo se purificó mediante una cromatografía en gel de sílice (CH₂Cl₂/MeOH 1:0->10:1) para producir el producto como un sólido blanco.

15

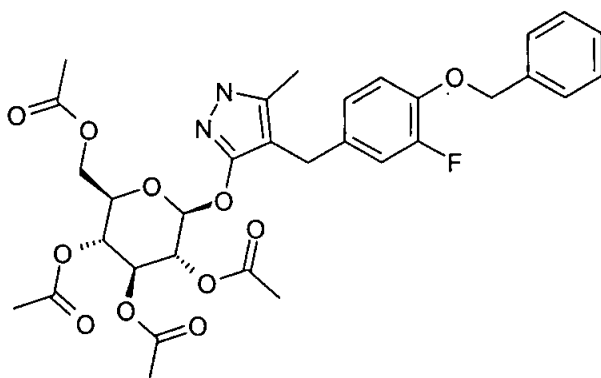
Rendimiento: 0,40 g (28%).

ESI-EM: m/z = 645 [M+H]⁺

Los siguientes compuestos pueden obtenerse de una forma similar:

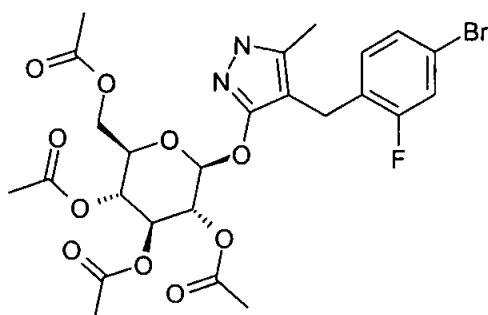
- 55 -

- (1) 4-(4-benciloxi-3-fluorobencil)-5-metil-3-(2,3,4,6-tetra-O-acetil-β-D-glucopiranos-1-iloxi)-1H-pirazol



ESI-EM: $m/z = 643 [M+H]^+$

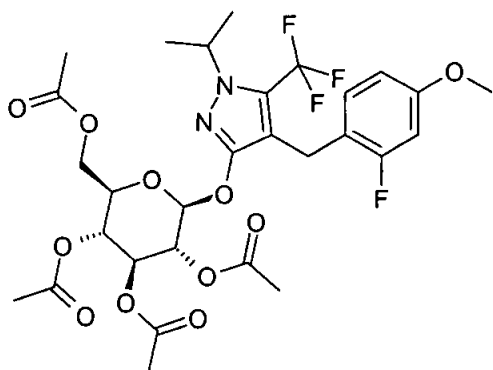
- 5 (2) 4-(4-bromo-2-fluorobencil)-5-metil-3-(2,3,4,6-tetra-O-acetil-β-D-glucopiranos-1-iloxi)-1H-pirazol



R_f 0,46 (gel de sílice, hexano/EtOAc 1:1)

Ejemplo XVIII

- 10 4-(2-fluoro-4-metoxibencil)-5-trifluorometil-3-(2,3,4,6-tetra-O-acetil-β-D-glucopiranos-1-iloxi)-1H-pirazol



A una disolución de 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-trifluorometil-1H-pirazol-3-ol (1,84 g, 5,54 mmol), K_2CO_3 (7,5 g, 54,3 mmol) y nBu_3BnNCl (0,25 g, 0,8

mmol) en agua (5 ml) y CH_2Cl_2 (25 ml) se le añadió bromuro de 2,3,4,6-tetra-O-acetil- β -D-glucopiranos-1-ilo (3,80 g, 8,78 mmol). La mezcla de reacción se agitó vigorosamente a temperatura ambiente en la oscuridad durante la noche. Después se añadió CH_2Cl_2 y la capa orgánica se separó. Después de lavar con agua y ácido

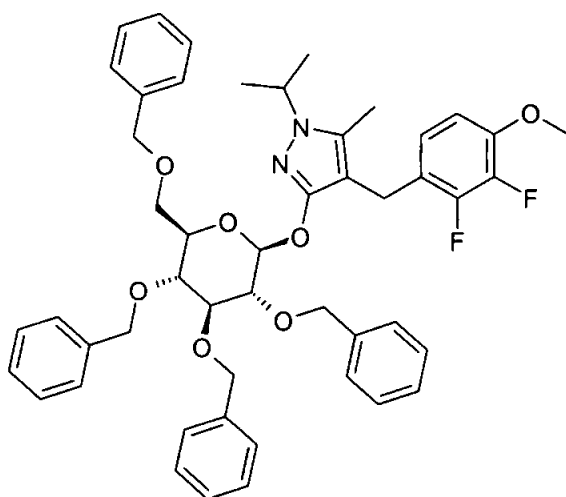
5 fosfórico 1 M, la fase orgánica se secó sobre Na_2SO_4 , y se eliminó el disolvente. El residuo se purificó mediante una cromatografía en gel de sílice (ciclohexano/EtOAc 3:2->0:1).

Rendimiento: 2,42 g (con una pureza de aprox. 50%).

ESI-EM: $m/z = 663$ $[\text{M}+\text{H}]^+$

10 Ejemplo XIX

4-(2,3-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-(2,3,4,6-tetra-O-bencil- β -D-glucopiranos-1-ilo)-1H-pirazol



A una mezcla a 20 °C de 4-(2,3-difluoro-4-metoxibencil)-5-metil-3-(2,3,4,6-tetra-O-bencil- β -D-glucopiranos-1-ilo)-1H-pirazol (2,90 g, 3,7 mmol) y Cs_2CO_3 (12,30 g, 37,8 mmol) en DMF (56 ml) se le añadió yoduro de isopropilo (1,90 ml, 18,9 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2,5 h. Después la mezcla de reacción después se vertió en agua (300 ml), y la disolución resultante se extrajo con EtOAc. Los extractos orgánicos reunidos se lavaron con agua y salmuera, y se

15 secaron sobre MgSO_4 . La disolución orgánica se concentró a 40 °C a presión reducida, y el residuo se purificó mediante una cromatografía en gel de sílice (ciclohexano/EtOAc 6:1->1:1).

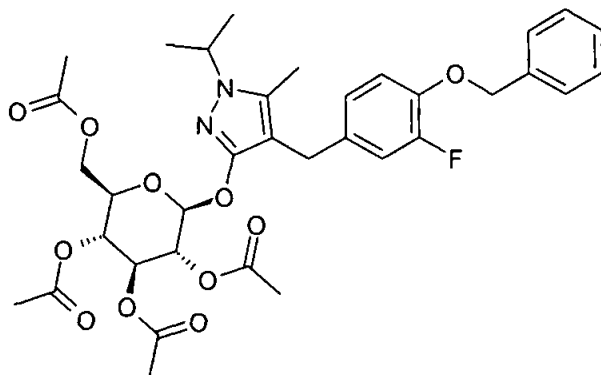
Rendimiento: 2,10 g (69%).

ESI-EM: $m/z = 459$ $[\text{M}+\text{H}]^+$

25 Los siguientes compuestos pueden obtenerse de una forma similar:

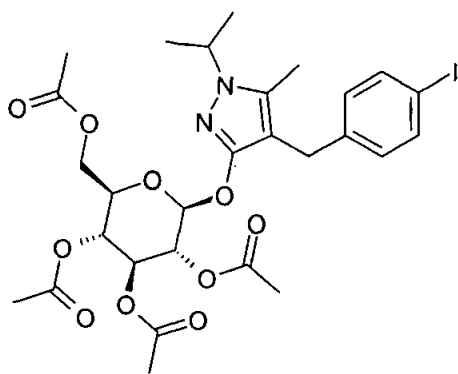
- 57 -

- (1) 4-(4-benciloxi-3-fluorobencil)-1-isopropil-5-metil-3-(2,3,4,6-tetra-O-acetil-β-D-glucopiranos-1-iloxi)-1H-pirazol



ESI-EM: $m/z = 685 [M+H]^+$

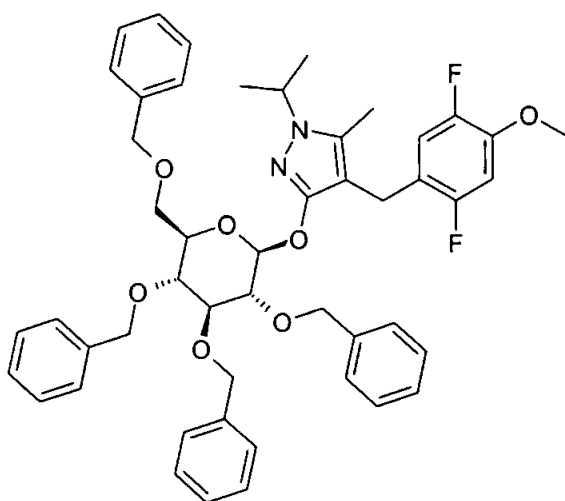
- 5 (2) 4-(4-yodobencil)-1-isopropil-5-metil-3-(2,3,4,6-tetra-O-acetil-β-D-glucopiranos-1-iloxi)-1H-pirazol



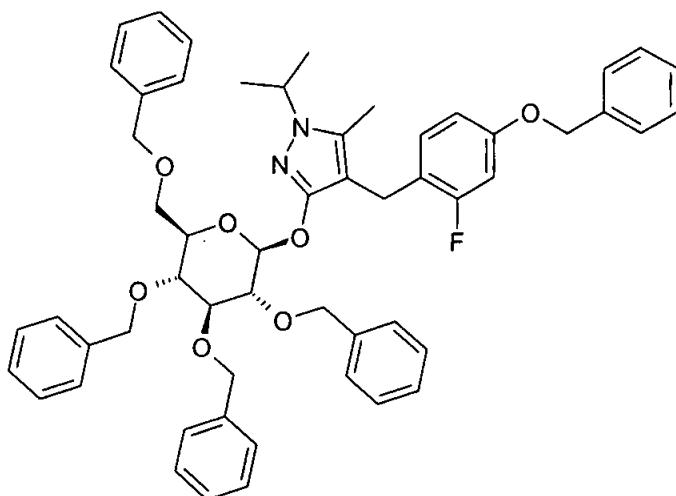
ESI-EM: $m/z = 687 [M+H]^+$

- 10 (3) 4-(2,5-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-(2,3,4,6-tetra-O-bencil-β-D-glucopiranos-1-iloxi)-1H-pirazol

- 58 -

ESI-EM: $m/z = 819$ $[M+H]^+$

(4) 4-(2-fluoro-4-benzyloxyphenyl)-1-isopropyl-5-metil-3-(2,3,4,6-tetra-O-bencil-β-D-glucopiranos-1-iloxi)-1H-pirazol

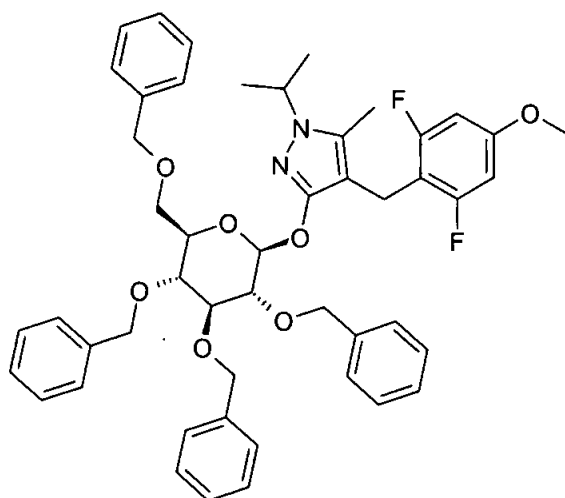


5

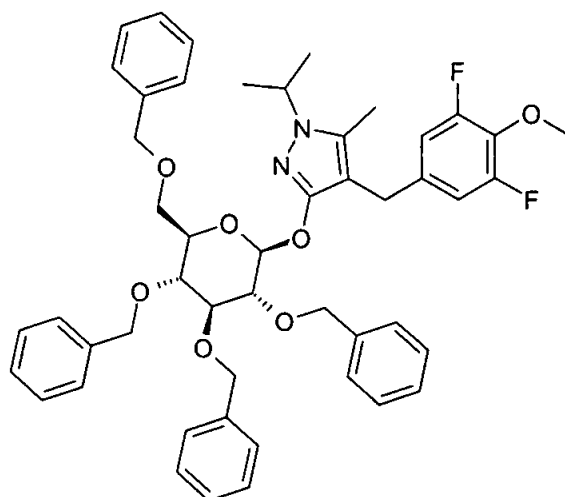
ESI-EM: $m/z = 877$ $[M+H]^+$

(5) 4-(2,6-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-(2,3,4,6-tetra-O-bencil-β-D-glucopiranos-1-iloxi)-1H-pirazol

- 59 -

ESI-EM: $m/z = 819$ $[M+H]^+$

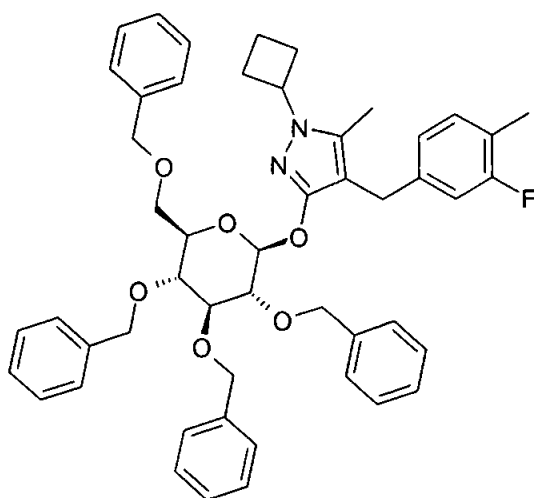
(6) 4-(3,5-difluoro-4-methoxybenzyl)-1-isopropyl-5-metil-3-(2,3,4,6-tetra-O-bencil-β-D-glucopiranos-1-iloxi)-1H-pirazol



5

ESI-EM: $m/z = 819$ $[M+H]^+$

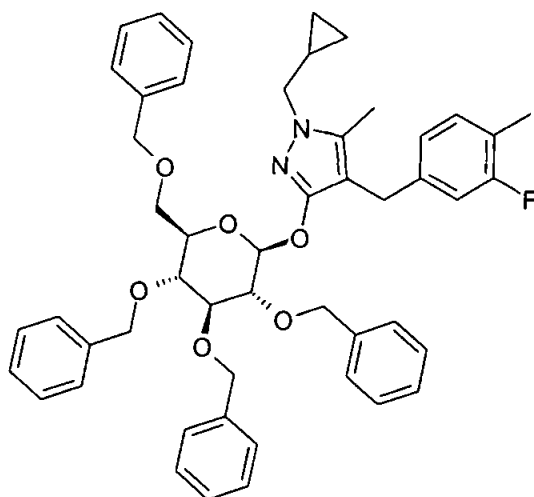
(7) 1-ciclobutil-4-(3-fluoro-4-metilbencil)-5-metil-3-(2,3,4,6-tetra-O-bencil-β-D-glucopiranos-1-iloxi)-1H-pirazol



Se utilizó bromociclobutano como electrófilo en lugar de yoduro de isopropilo.

ESI-EM: $m/z = 797$ $[M+H]^+$

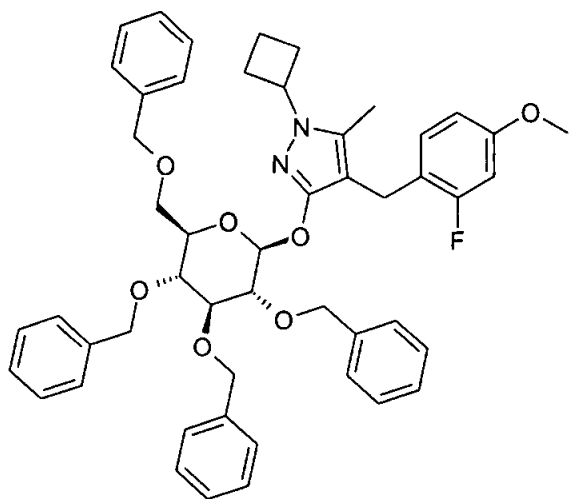
- (8) 1-ciclopropilmetil-4-(3-fluoro-4-metilbencil)-5-metil-3-(2,3,4,6-tetra-O-bencil- β -D-glucopiranos-1-iloxi)-1H-pirazol



Se obtuvo como producto secundario en la preparación del ejemplo XVIII(7).

ESI-EM: $m/z = 797$ $[M+H]^+$

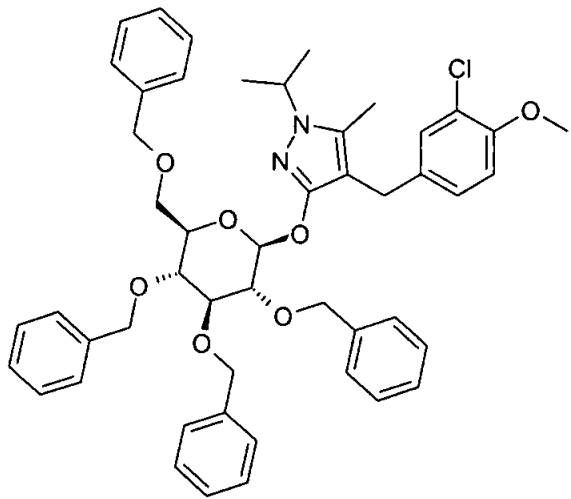
- (9) 1-ciclobutil-4-(2-fluoro-4-metoxibencil)-5-metil-3-(2,3,4,6-tetra-O-bencil- β -D-glucopiranos-1-iloxi)-1H-pirazol



Se utilizó bromociclobutano como electrófilo en lugar de yoduro de isopropilo.

ESI-EM: m/z = 813 [M+H]⁺

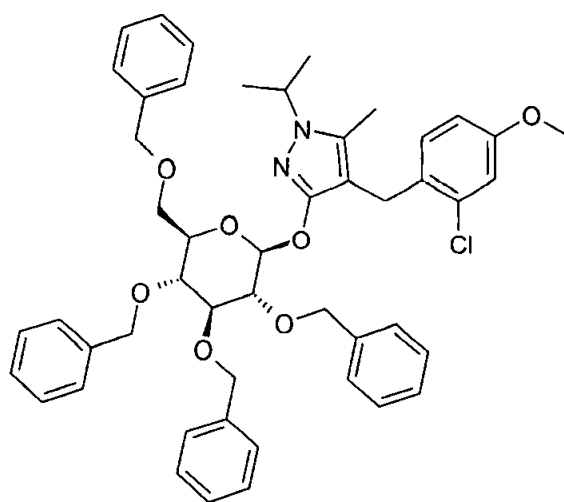
- (10) 4-(3-cloro-4-metoxibencil)-1-isopropil-5-metil-3-(2,3,4,6-tetra-O-bencil-β-D-glucopiranos-1-iloxi)-1H-pirazol
- 5



La reacción se realiza preferiblemente con hexametildisilazida de potasio como base en tolueno y THF.

ESI-EM: m/z = 817/819 [M+H]⁺ (cloro)

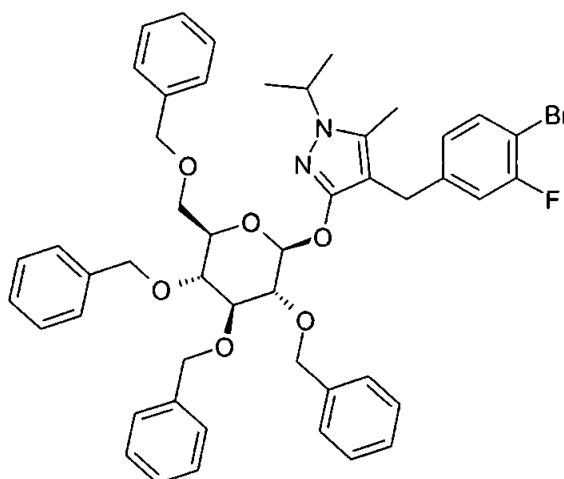
- 10 (11) 4-(2-cloro-4-metoxibencil)-1-isopropil-5-metil-3-(2,3,4,6-tetra-O-bencil-β-D-glucopiranos-1-iloxi)-1H-pirazol



La reacción se realiza preferiblemente con hexametildisilazida de potasio como base en tolueno y THF.

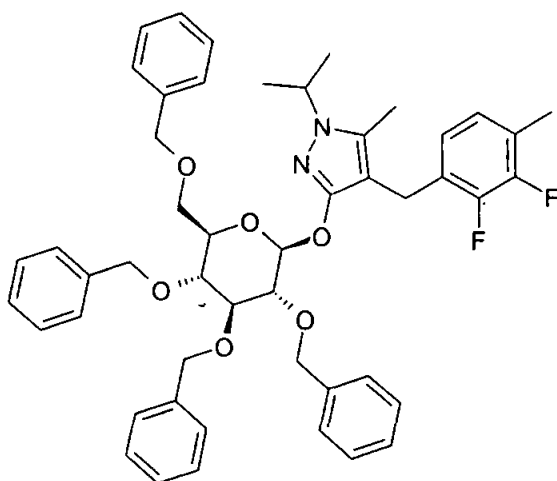
ESI-EM: $m/z = 817/819$ $[M+H]^+$ (cloro)

- 5 (12) 4-(4-bromo-3-fluorobencil)-1-isopropil-5-metil-3-(2,3,4,6-tetra-O-bencil- β -D-glucopiranos-1-iloxi)-1H-pirazol



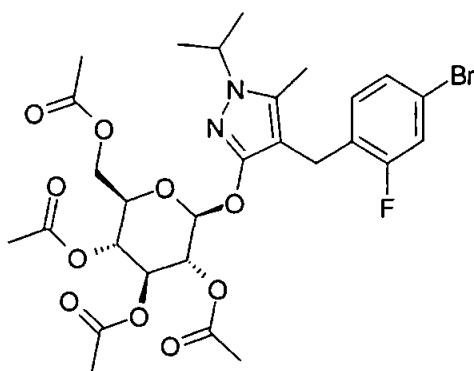
- (13) 4-(2,3-difluoro-4-metilbencil)-1-isopropil-5-metil-3-(2,3,4,6-tetra-O-bencil- β -D-glucopiranos-1-iloxi)-1H-pirazol

- 63 -



R_f 0,65 (gel de sílice, hexano/EtOAc 1:1)

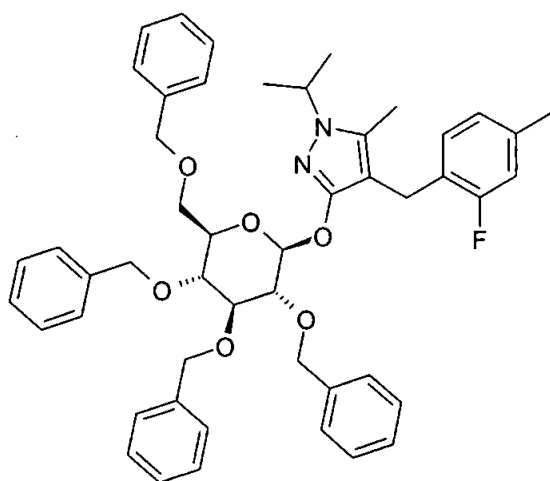
(14) 4-(4-bromo-2-fluorobenzil)-1-isopropil-5-metil-3-(2,3,4,6-tetra-O-acetil-β-D-glucopiranos-1-iloxi)-1H-pirazol



5

R_f 0,50 (gel de sílice, hexano/EtOAc 1:1)

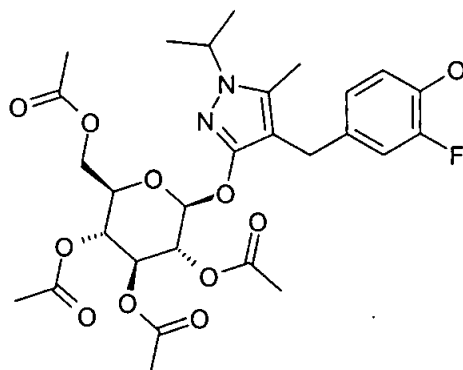
(15) 4-(2-fluoro-4-metilbencil)-1-isopropil-5-metil-3-(2,3,4,6-tetra-O-bencil-β-D-glucopiranos-1-iloxi)-1H-pirazol



R_f 0,53 (gel de sílice, hexano/EtOAc 4:1)

Ejemplo XX

4-(3-fluoro-4-hidroxibencil)-1-isopropil-5-metil-3-(2,3,4,6-tetra-O-acetil-β-D-glucopiranos-1-iloxi)-1H-pirazol



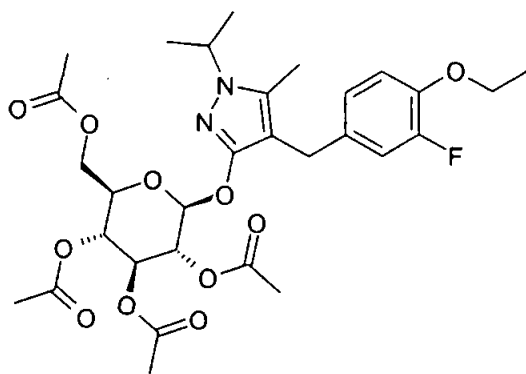
Una mezcla de 4-(4-benciloxi-3-fluorobencil)-1-isopropil-5-metil-3-(2,3,4,6-tetra-O-acetil-β-D-glucopiranos-1-iloxi)-1H-pirazol (0,26 g, 0,38 mmol) y Pd al 10% sobre carbono (0,05 g) en EtOAc (10 ml) se agitó a temperatura ambiente bajo una atmósfera de hidrógeno (3 bar). Después de 3 h se separó el catalizador mediante filtración, y el disolvente se eliminó a presión reducida. El residuo se disolvió en Et₂O, se filtró sobre Celite®, y se concentró al vacío.

Rendimiento: 0,22 g (97%).

ESI-EM: m/z = 595 [M+H]⁺

Ejemplo XXI

4-(3-fluoro-4-etoxibencil)-1-isopropil-5-metil-3-(2,3,4,6-tetra-O-acetil-β-D-glucopiranos-1-iloxi)-1H-pirazol



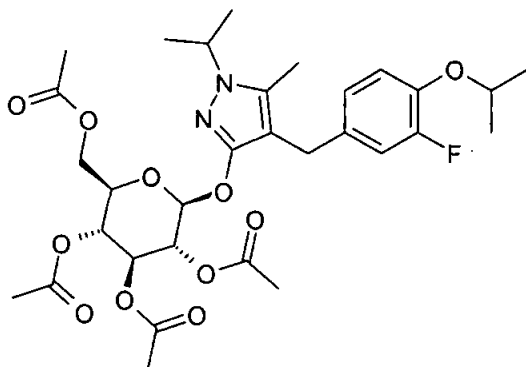
A una suspensión de 4-(3-fluoro-4-hidroxibencil)-1-isopropil-5-metil-3-(2,3,4,6-tetra-O-acetil-β-D-glucopiranos-1-iloxi)-1H-pirazol (0,22 g, 0,37 mmol) y carbonato de cesio (0,31 g, 0,40 mmol) en DMF (3 ml) se le añadió bromuro de etilo (30 μl, 0,40 mmol). Después de agitar a temperatura ambiente durante 5 h, la mezcla se vertió en una mezcla de EtOAc y ácido fosfórico (0,1 M). La fase orgánica se separó, se lavó con una disolución acuosa de NaHCO₃ y salmuera, y se secó sobre Na₂SO₄. La disolución orgánica se concentró, y el residuo se purificó mediante una cromatografía en gel de sílice (éter de petróleo/EtOAc 1:1).

10 Rendimiento: 0,18 g (78%).

ESI-EM: m/z = 623 [M+H]⁺

El siguiente compuesto puede obtenerse de una forma similar:

(1) 4-(3-fluoro-4-isopropoxibencil)-1-isopropil-5-metil-3-(2,3,4,6-tetra-O-acetil-β-D-glucopiranos-1-iloxi)-1H-pirazol

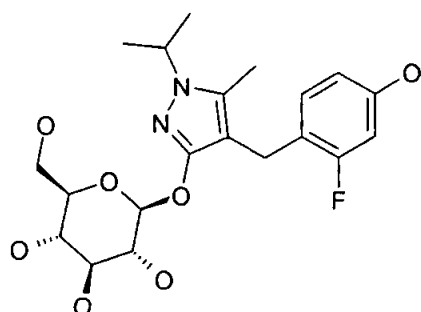


15

ESI-EM: m/z = 637 [M+H]⁺

Ejemplo XXII

4-(2-fluoro-4-hidroxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol



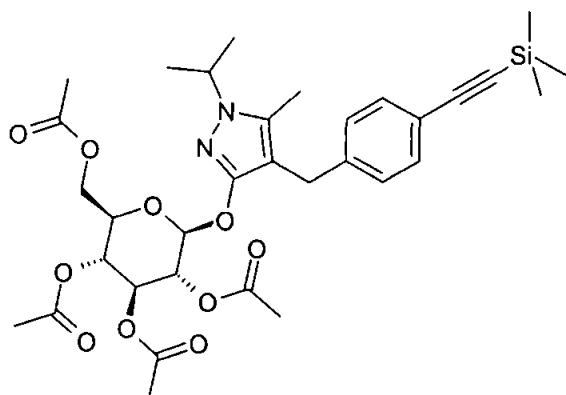
Una mezcla de 4-(2-fluoro-4-benzyloxibenzyl)-1-isopropil-5-metil-3-(2,3,4,6-tetra-O-bencil-β-D-glucopiranos-1-iloxi)-1H-pirazol (2,0 g, 2,3 mmol) y Pd al 20% sobre carbono (1,0 g) en EtOH (70 ml) se agitó a temperatura ambiente bajo una atmósfera de hidrógeno (344,737 kPa). Después de 2 h se separó el catalizador mediante filtración, y el disolvente se eliminó a presión reducida. El residuo se purificó mediante una cromatografía en gel de sílice (CH₂Cl₂/MeOH 10:1→3:1).

Rendimiento: 0,69 g (71%).

ESI-EM: m/z = 427 [M+H]⁺

10 Ejemplo XXIII

4-(4-trimetilsililetilbencil)-1-isopropil-5-metil-3-(2,3,4,6-tetra-O-acetil-β-D-glucopiranos-1-iloxi)-1H-pirazol



A una disolución desgasificada de 4-(4-yodobencil)-1-isopropil-5-metil-3-(2,3,4,6-tetra-O-acetil-β-D-glucopiranos-1-iloxi)-1H-pirazol (0,31 g, 0,45 mmol) en DMF (5 ml) bajo una atmósfera de Ar se le añadió, en el orden indicado, NEt₃ (0,2 ml, 1,43 mmol), CuI (0,02 g, 0,11 mmol), (Ph₃P)₂PdCl₂ (0,05 g, 0,07 mmol) y trimetilsililacetileno (0,10 ml, 0,69 mmol). La mezcla de reacción se agitó a 90 °C durante 3,5 h. Después de enfriar hasta la temperatura ambiente se añadió EtOAc, y la disolución resultante se lavó con una disolución acuosa de NaHCO₃ y se secó sobre Na₂SO₄. El disolvente

se evaporó, y el residuo se purificó mediante una cromatografía en gel de sílice (ciclohexano/EtOAc, 9:1 ->1:1) para producir el producto como un aceite amarillo.

Rendimiento: 0,18 g (64%).

ESI-EM: $m/z = 657$ $[M+H]^+$

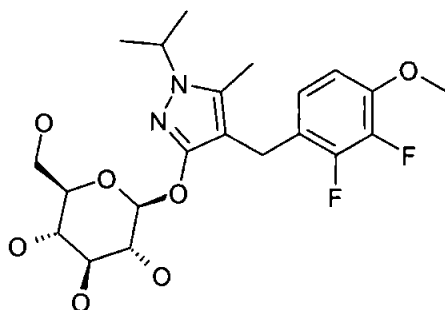
5

Preparación de los productos

Ejemplo 1

(1) 4-(2,3-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol

10



Una mezcla de 4-(2,3-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-(2,3,4,6-tetra-O-bencil-β-D-glucopiranos-1-iloxi)-1H-pirazol (1,80 g, 2,2 mmol) y Pd al 20% sobre carbono (1 g) en EtOH (50 ml) se agitó a temperatura ambiente bajo una atmósfera de hidrógeno (344,737 kPa). Después de 2,5 h se separó el catalizador mediante filtración, y el disolvente se eliminó a presión reducida. El residuo se purificó mediante una cromatografía en gel de sílice (DCM/MeOH 1:0->4:1) para producir el producto como un sólido blanco.

15

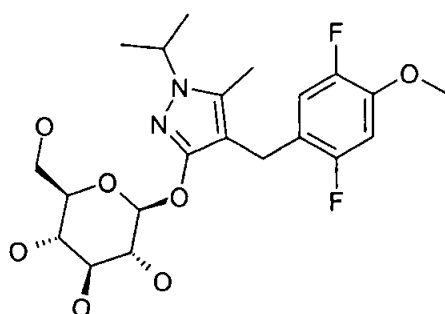
Rendimiento: 0,48 g (48%).

20 ESI-EM: $m/z = 459$ $[M+H]^+$

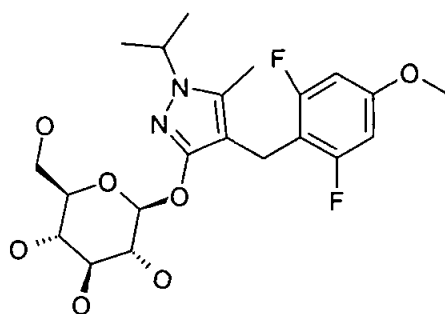
Los siguientes compuestos pueden obtenerse de una forma similar:

(2) 4-(2,5-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol

- 68 -

ESI-EM: $m/z = 459$ $[M+H]^+$

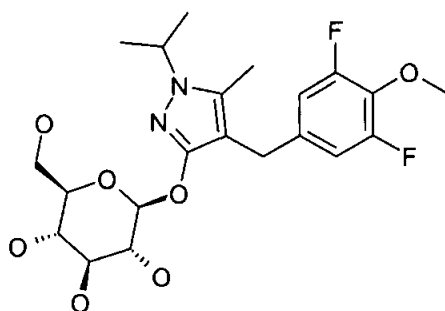
(3) 4-(2,6-difluoro-4-methoxybenzyl)-1-isopropyl-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol



5

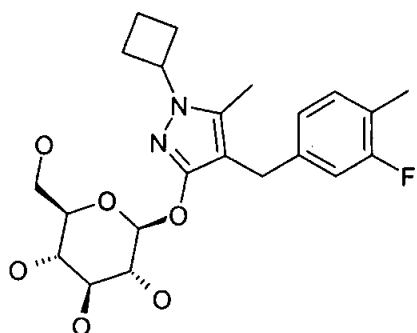
ESI-EM: $m/z = 459$ $[M+H]^+$

(4) 4-(3,5-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol

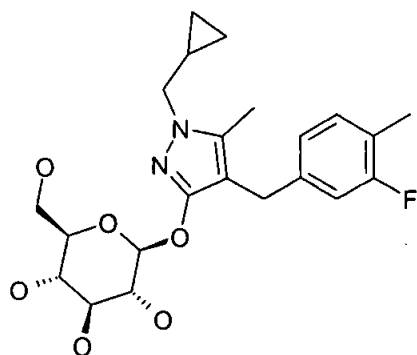
10 ESI-EM: $m/z = 459$ $[M+H]^+$

(5) 1-ciclobutil-4-(3-fluoro-4-metilbencil)-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol

- 69 -

ESI-EM: $m/z = 437$ $[M+H]^+$

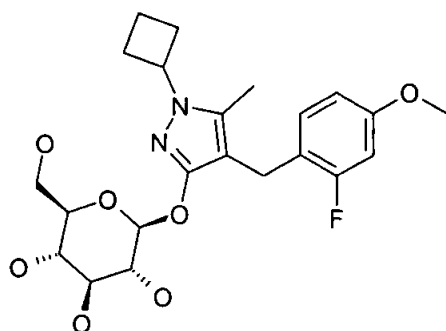
(6) 1-ciclopropilmetil-4-(3-fluoro-4-metilbencil)-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol



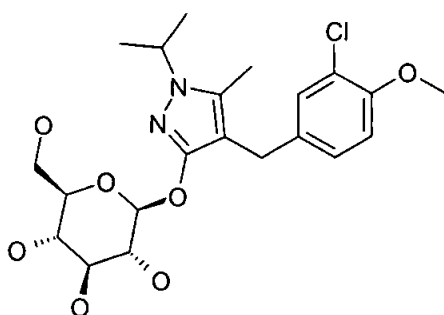
5

ESI-EM: $m/z = 437$ $[M+H]^+$

(7) 1-ciclobutil-4-(2-fluoro-4-metoxibencil)-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol

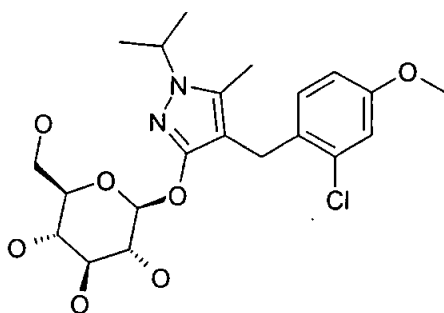
ESI-EM: $m/z = 453$ $[M+H]^+$

10 (8) 4-(3-cloro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol



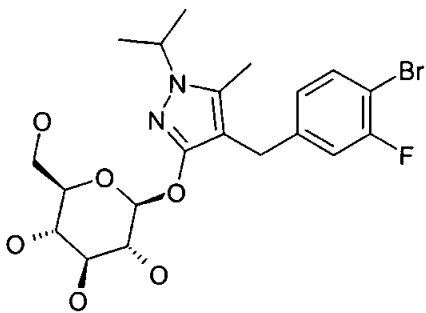
ESI-EM: $m/z = 457/459$ $[M+H]^+$ (cloro)

(9) 4-(2-cloro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol



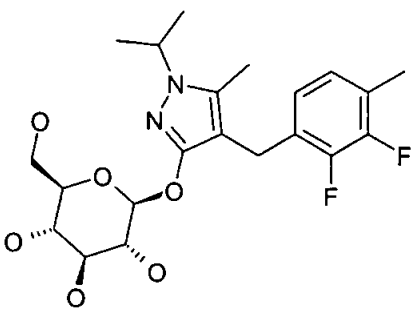
5 ESI-EM: $m/z = 457/459$ $[M+H]^+$ (cloro)

(10) 4-(4-bromo-3-fluorobencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol



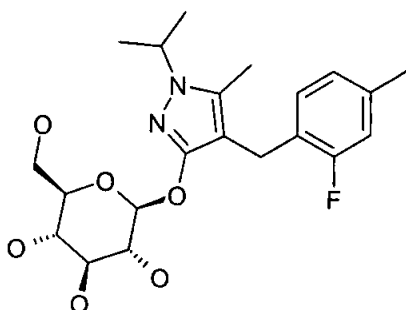
(11) 4-(2,3-difluoro-4-metilbencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol

10



R_f 0,24 (gel de sílice, CHCl₃/MeOH 9:1)

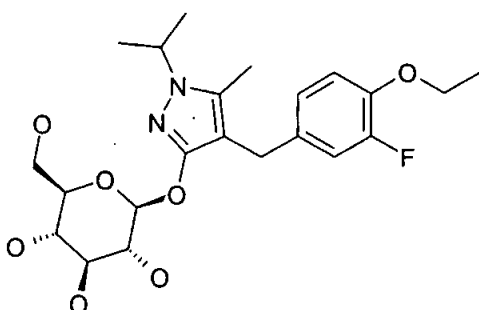
(12) 4-(2-fluoro-4-metilbencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol



R_f 0,24 (gel de sílice, CH₂Cl₂/MeOH 9:1)

5 Ejemplo 2

(13) 4-(3-fluoro-4-etoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol



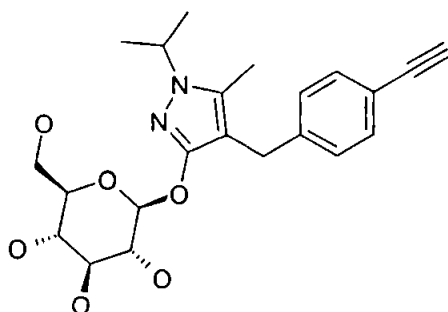
A una disolución enfriada en hielo de 4-(4-etoxi-3-fluorobencil)-1-isopropil-5-metil-3-(2,3,4,6-tetra-O-acetil-β-D-glucopiranos-1-iloxi)-1H-pirazol (0,17 g, 0,27 mmol) en MeOH (1 ml) y THF (1,5 ml) se le añadió una disolución acuosa de LiOH (1 M, 1,25 ml). La disolución se agitó en el baño de hielo durante 1 h y después se diluyó con EtOAc y agua. Se separó la fase orgánica, se lavó con agua y salmuera, y se secó sobre Na₂SO₄. Se retiró el disolvente y el residuo se secó al vacío para producir el producto como una espuma blanca.

15 Rendimiento: 0,12 g (95%).

ESI-EM: m/z = 455 [M+H]⁺

Los siguientes compuestos pueden obtenerse de una forma similar:

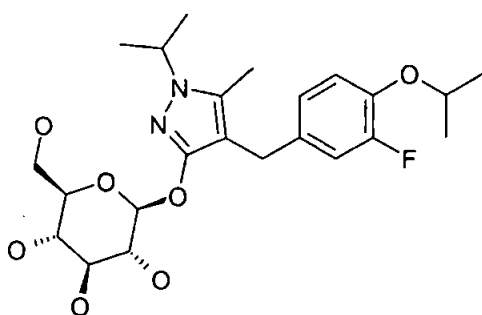
(14) 4-(4-etinilbencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol



El 4-(4-trimetilsililetinilbencil)-1-isopropil-5-metil-3-(2,3,4,6-tetra-O-acetil- β -D-glucopiranos-1-iloxi)-1H-pirazol se sometió a las condiciones de reacción descritas anteriormente.

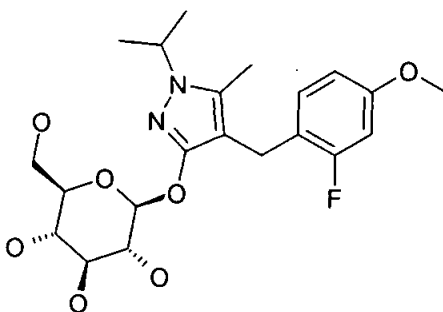
5 ESI-EM: $m/z = 417 [M+H]^+$

(15) 4-(3-fluoro-4-isopropoxibencil)-1-isopropil-5-metil-3- β -D-glucopiranos-1-iloxi-1H-pirazol

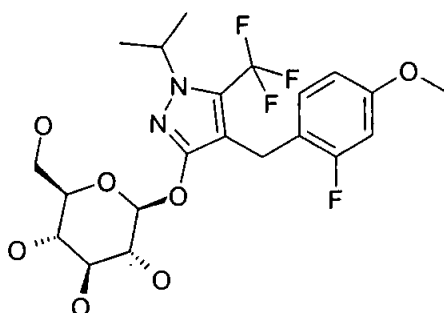


ESI-EM: $m/z = 469 [M+H]^+$

10 (16) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-metil-3- β -D-glucopiranos-1-iloxi-1H-pirazol

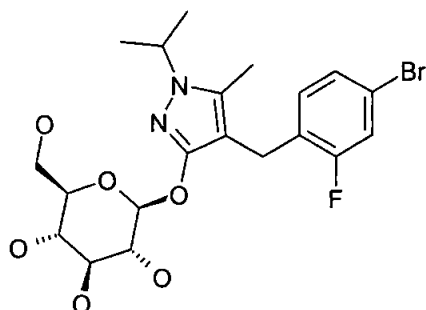


(17) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-trifluorometil-3- β -D-glucopiranos-1-iloxi-1H-pirazol



ESI-EM: $m/z = 495 [M+H]^+$

(18) 4-(4-bromo-2-fluorobenzyl)-1-isopropyl-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol

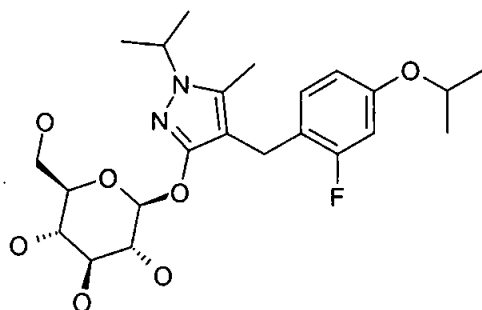


5

R_f 0,29 (gel de sílice, $CH_2Cl_2/MeOH$ 9:1)

Ejemplo 3

(19) 4-(2-fluoro-4-isopropoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol



10

A una suspensión de 4-(2-fluoro-4-hidroxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol (0,20 g, 0,47 mmol) y carbonato de cesio (0,16 g, 0,50 mmol) en DMF (3,5 ml) se le añadió yoduro de isopropilo (52 μl, 0,50 mmol). Después de agitar la mezcla a temperatura ambiente durante la noche, se añadió otra porción de carbonato de cesio (0,10 g) y yoduro de isopropilo (30 μl). Después de agitar otras 24 h a temperatura ambiente, la mezcla se diluyó con EtOAc, ácido fosfórico (0,1 M) y salmuera. Se separó la fase orgánica, se lavó con salmuera y se secó sobre Na_2SO_4 .

15

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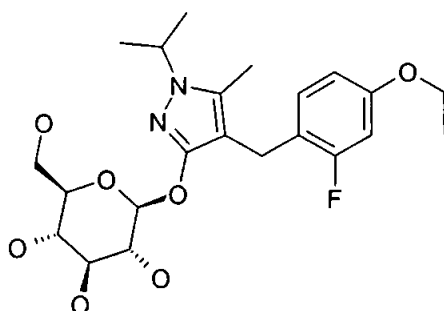
La disolución orgánica se concentró, y el residuo se purificó mediante una cromatografía en gel de sílice (DCM/MeOH, 10:1) para producir el producto como una espuma blanca.

Rendimiento: 0,16 g (73%).

5 ESI-EM: $m/z = 469 [M+H]^+$

El siguiente compuesto puede obtenerse de una forma similar:

(20) 4-(2-fluoro-4-etoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol



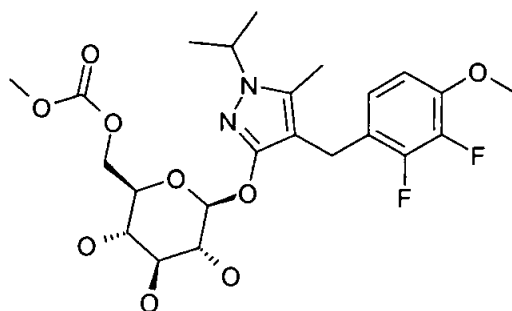
ESI-EM: $m/z = 455 [M+H]^+$

10 Los compuestos (21) a (29) pueden obtenerse mediante métodos como los descritos en esta solicitud o en la bibliografía.

Ejemplo 4

(30a) 4-(2,3-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-metoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol

15



20 A una disolución enfriada en hielo de 4-(2,3-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol (0,23 g, 0,50 mmol) en 2,4,6-trimetilpiridina (0,7 ml) se le añadió cloroformiato de metilo (42 μl, 0,55 mmol). La disolución de reacción se calentó en el baño de hielo hasta alcanzar la temperatura ambiente y se agitó durante la noche. Después la disolución se diluyó con Et₂O, se lavó con HCl acuoso (1 M) y salmuera, y se secó sobre MgSO₄. El disolvente se

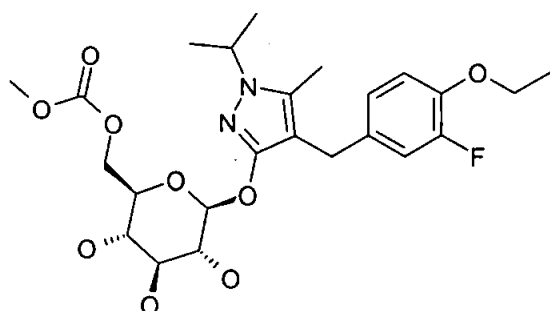
evaporó, y el residuo se purificó mediante una cromatografía en gel de sílice (DCM/MeOH, 25:1->1:3) para producir el producto como un sólido blanco.

Rendimiento: 0,15 g (56%).

ESI-EM: $m/z = 517 [M+H]^+$

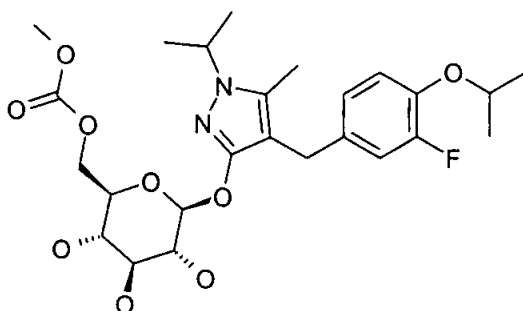
5 Los siguientes compuestos pueden obtenerse de una forma similar:

(31a) 4-(3-fluoro-4-etoxibencil)-1-isopropil-5-metil-3-(6-O-metoxycarbonil- β -D-glucopiranos-1-iloxi)-1H-pirazol



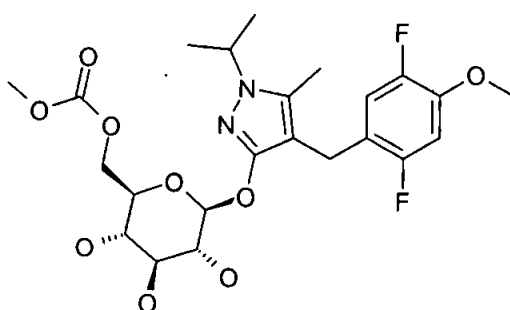
ESI-EM: $m/z = 513 [M+H]^+$

10 (32a) 4-(3-fluoro-4-isopropoxibencil)-1-isopropil-5-metil-3-(6-O-metoxycarbonil- β -D-glucopiranos-1-iloxi)-1H-pirazol



ESI-EM: $m/z = 527 [M+H]^+$

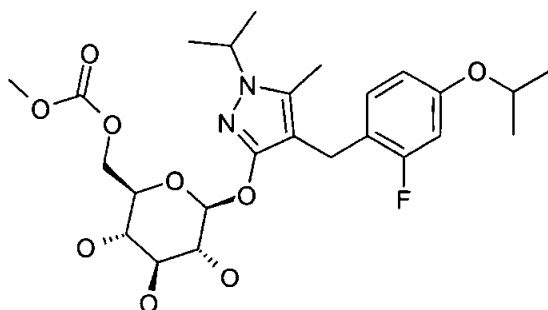
15 (33a) 4-(2,5-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-metoxycarbonil- β -D-glucopiranos-1-iloxi)-1H-pirazol



ESI-EM: $m/z = 517 [M+H]^+$

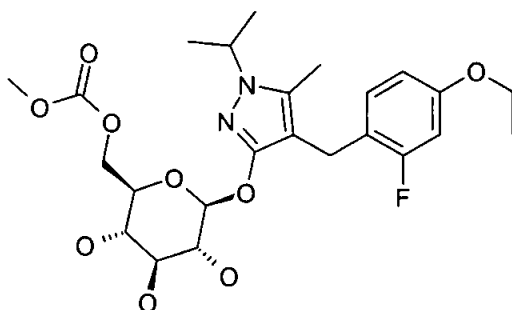
- 76 -

(34a) 4-(2-fluoro-4-isopropoxybencil)-1-isopropil-5-metil-3-(6-O-metoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol



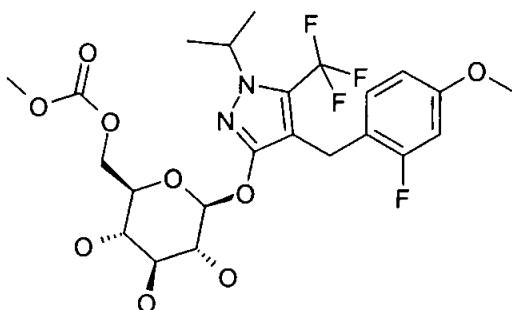
ESI-EM: m/z = 527 [M+H]⁺

5 (35a) 4-(2-fluoro-4-ethoxybencil)-1-isopropil-5-metil-3-(6-O-metoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol



ESI-EM: m/z = 513 [M+H]⁺

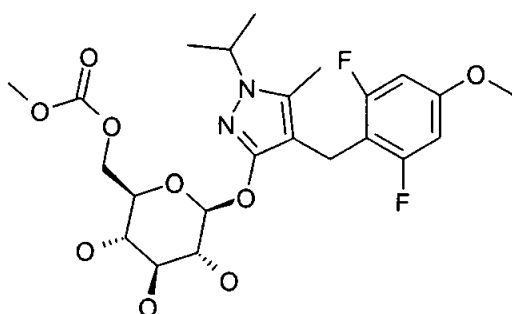
10 (36a) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-trifluorometil-3-(6-O-metoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol



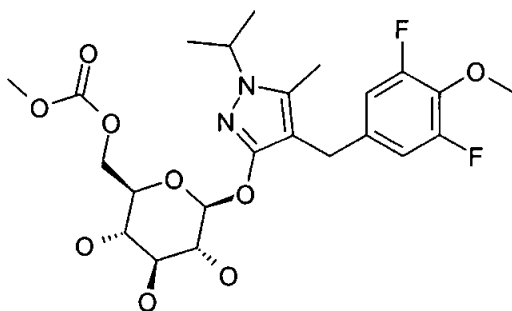
ESI-EM: m/z = 553 [M+H]⁺

(37a) 4-(2,6-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-metoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol

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ESI-EM: $m/z = 517$ $[M+H]^+$

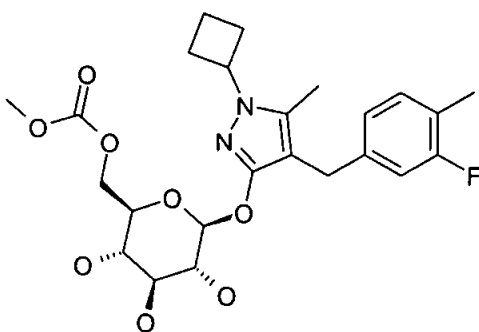
(38a) 4-(3,5-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-metoxicarbonil- β -D-glucopiranos-1-iloxi)-1H-pirazol



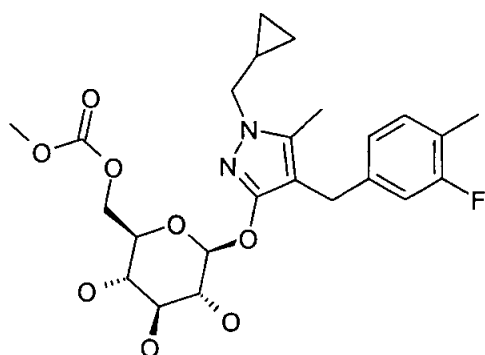
5

ESI-EM: $m/z = 517$ $[M+H]^+$

(39a) 1-ciclobutil-4-(3-fluoro-4-metilbencil)-5-metil-3-(6-O-metoxicarbonil- β -D-glucopiranos-1-iloxi)-1H-pirazol

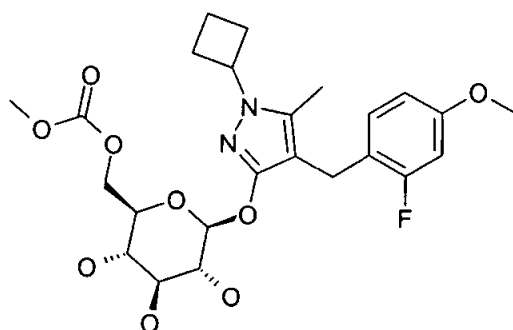
10 ESI-EM: $m/z = 495$ $[M+H]^+$

(40a) 1-ciclopropilmetil-4-(3-fluoro-4-metilbencil)-5-metil-3-(6-metoxicarbonil- β -D-glucopiranos-1-iloxi)-1H-pirazol



ESI-EM: $m/z = 495 [M+H]^+$

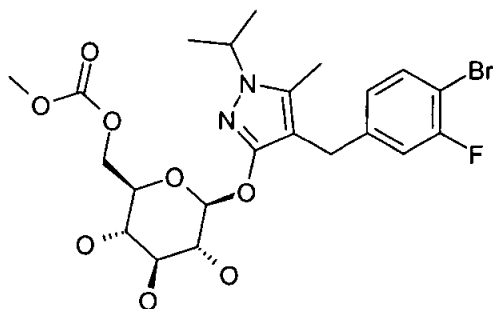
(41a) 1-ciclobutil-4-(2-fluoro-4-metoxibencil)-5-metil-3-(6-O-metoxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol



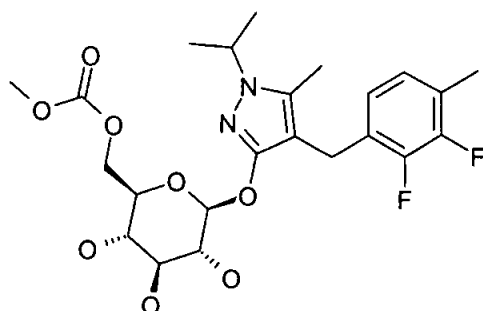
5

ESI-EM: $m/z = 511 [M+H]^+$

(42a) 4-(4-bromo-3-fluorobencil)-1-isopropil-5-metil-3-(6-O-metoxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol

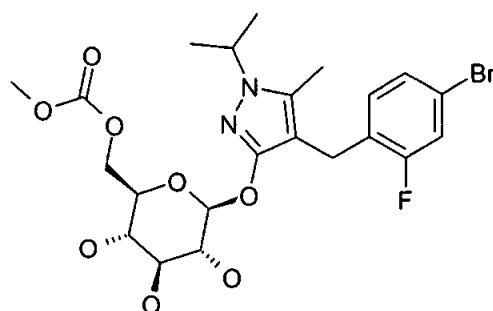


10 (43a) 4-(2,3-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-metoxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol



R_f 0,49 (gel de sílice, CHCl₃/MeOH 10:1)

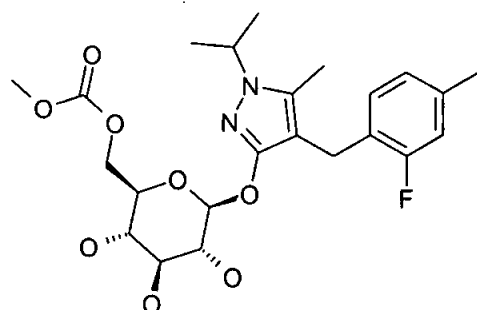
(44a) 4-(4-bromo-2-fluorobencil)-1-isopropil-5-metil-3-(6-O-metoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol



5

R_f 0,39 (gel de sílice, CH₂Cl₂/MeOH 19:1)

(45a) 4-(2-fluoro-4-metilbencil)-1-isopropil-5-metil-3-(6-O-metoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol



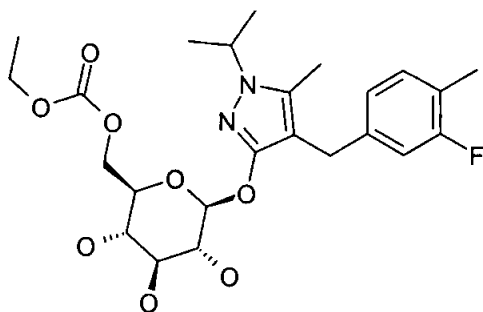
10 R_f 0,62 (gel de sílice, CH₂Cl₂/MeOH 9:1)

Los compuestos (30b), (31b), (32b), (33b), (34b), (35b), (36b), (37b), (38b), (39b), (40b), (41b), (42b), (43b), (44b) y (45b) se obtienen de una manera análoga.

Ejemplo 5:

(46) 4-(3-fluoro-4-metilbencil)-1-isopropil-5-metil-3-(6-O-etoxycarbonil-β-D-

15 glucopiranos-1-iloxi)-1H-pirazol



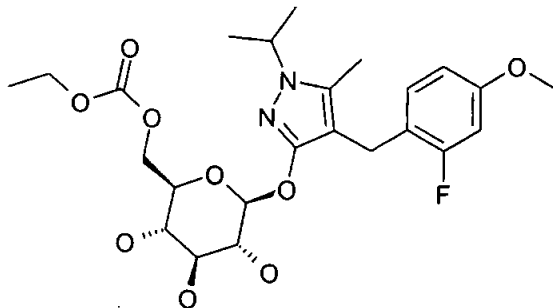
A una disolución enfriada en hielo de 4-(3-fluoro-4-metilbencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol (0,30 g, 0,70 mmol) en 2,4,6-trimetilpiridina (1 ml) se le añadió cloroformiato de metilo (76 μl, 0,80 mmol). La disolución de
5 reacción se calentó en el baño de hielo hasta alcanzar la temperatura ambiente y se agitó durante la noche. Después la disolución se diluyó con Et₂O, se lavó con HCl acuoso (1 M) y salmuera, y se secó sobre MgSO₄. El disolvente se evaporó, y el residuo se purificó mediante una cromatografía en gel de sílice (DCM/MeOH, 25:1->1:3) para producir el producto como un sólido blanco.

10 Rendimiento: 0,23 g (66%).

ESI-EM: m/z = 497 [M+H]⁺

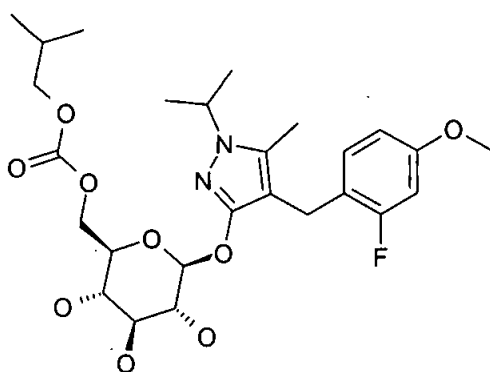
Los siguientes compuestos pueden obtenerse por analogía con el procedimiento descrito anteriormente:

(47) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-etoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol
15



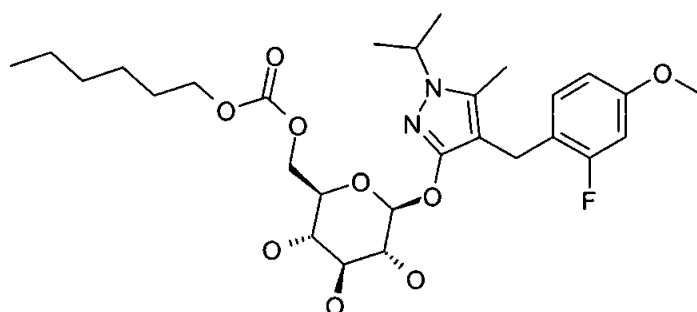
ESI-EM: m/z = 513 [M+H]⁺

(48) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-isobutiloxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol



ESI-EM: $m/z = 541$ $[M+H]^+$

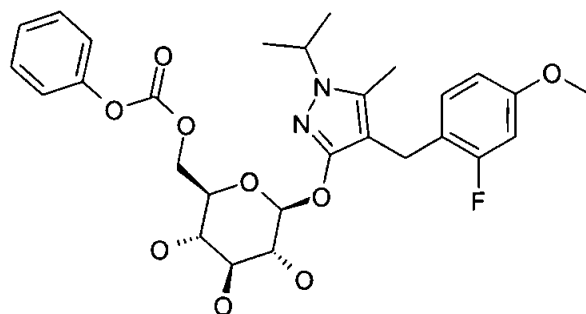
(49) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-hex-1-iloxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol



5

ESI-EM: $m/z = 569$ $[M+H]^+$

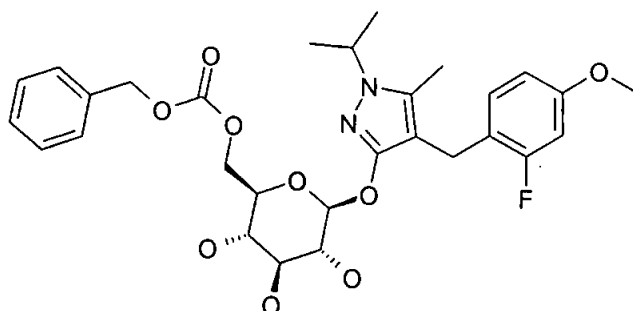
(50) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-fenoxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol



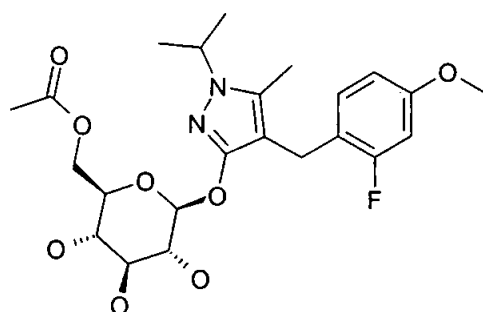
10 ESI-EM: $m/z = 561$ $[M+H]^+$

(51) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-benciloxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol

- 82 -

ESI-EM: $m/z = 575 [M+H]^+$

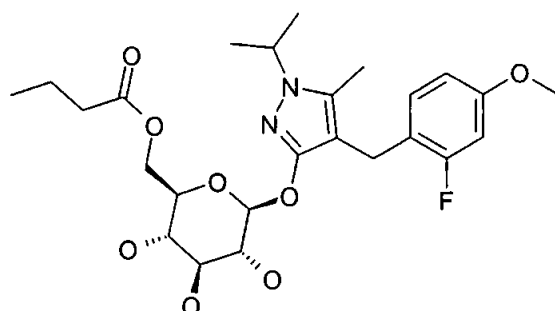
(52) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-acetil- β -D-glucopiranos-1-iloxi)-1H-pirazol



5

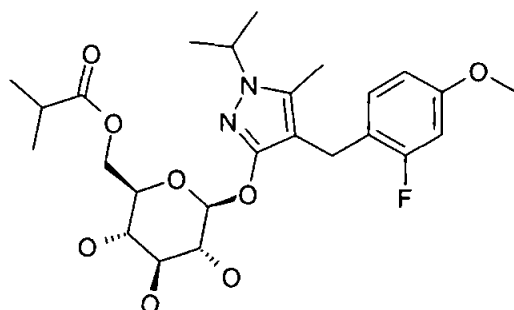
ESI-EM: $m/z = 483 [M+H]^+$

(53) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-propilcarbonil- β -D-glucopiranos-1-iloxi)-1H-pirazol

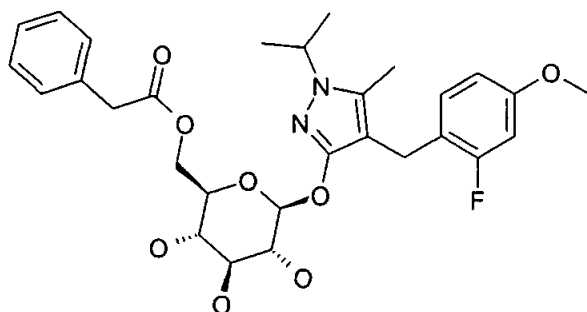
10 ESI-EM: $m/z = 511 [M+H]^+$

(54) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-isopropilcarbonil- β -D-glucopiranos-1-iloxi)-1H-pirazol

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ESI-EM: $m/z = 511 [M+H]^+$

(55) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-bencilcarbonil)- β -D-glucopiranos-1-iloxi)-1H-pirazol



5

ESI-EM: $m/z = 559 [M+H]^+$

Los compuestos (56) a (63) pueden obtenerse mediante analogía con el procedimiento descrito anteriormente.

REIVINDICACIONES

1. Un método para prevenir, frenar la progresión, retrasar o tratar un trastorno metabólico seleccionado del grupo que consiste en diabetes mellitus de tipo 1, diabetes mellitus de tipo 2, tolerancia alterada a la glucosa, hiperglucemia, hiperglucemia posprandial, sobrepeso, obesidad y síndrome metabólico en un paciente que lo necesite, que se caracteriza porque una composición farmacética que comprende un derivado de pirazol-O-glucósido seleccionado del grupo de compuestos (1) a (29) que consiste en

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- (1) 4-(2,3-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (2) 4-(2,5-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (3) 4-(2,6-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (4) 4-(3,5-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (5) 1-ciclobutil-4-(3-fluoro-4-metilbencil)-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (6) 1-ciclopropilmetil-4-(3-fluoro-4-metilbencil)-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (7) 1-ciclobutil-4-(2-fluoro-4-metoxibencil)-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (8) 4-(3-cloro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (9) 4-(2-cloro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (10) 4-(4-bromo-3-fluorobencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (11) 4-(2,3-difluoro-4-metilbencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (12) 4-(2-fluoro-4-metilbencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;

- (13) 4-(3-fluoro-4-etoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (14) 4-(4-etilbencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (15) 4-(3-fluoro-4-isopropoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (16) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (17) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-trifluorometil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (18) 4-(4-bromo-2-fluorobencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (19) 4-(2-fluoro-4-isopropoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (20) 4-(2-fluoro-4-etoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (21) 4-(4-etilbencil)-1-isopropil-5-trifluorometil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (22) 4-(4-bromobencil)-1-isopropil-5-trifluorometil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (23) 4-(4-etilbencil)-1-ciclobutil-5-trifluorometil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (24) 4-(4-etilbencil)-1-(2-fluoro-1-fluorometiletil)-5-trifluorometil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (25) 4-(3-fluoro-4-metoxibencil)-1-isopropil-5-trifluorometil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (26) 4-(3-fluoro-4-metilbencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (27) 4-(2,3-difluoro-4-isopropoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (28) 4-(3-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (29) 4-(4-etilbencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;

o su profármaco, en los que uno o más grupos hidroxilo del grupo β-D-glucopiranosilo se acilan con grupos seleccionados de (alquil C₁₋₁₈)carbonilo, (alquil C₁.

₁₈)oxycarbonilo, fenilcarbonilo, fenil-(alquil C₁₋₃)-carbonilo, feniloxycarbonilo, y fenil-(alquil C₁₋₃)-oxycarbonilo, o su sal farmacéuticamente aceptable, se administra.

2. Un método para mejorar el control glucémico y/o para reducir la glucosa plasmática en ayunas, la glucosa plasmática posprandial y/o la hemoglobina HbA1c glicosilada en un paciente que lo necesite, que se caracteriza porque se administra una composición farmacéutica que comprende un derivado de pirazol-O-glucósido seleccionado del grupo de compuestos (1) a (29), o su profármaco, o su sal farmacéuticamente aceptable, definido como en la reivindicación 1.

3. Un método para prevenir, frenar, retrasar o revertir la progresión desde la tolerancia alterada a la glucosa, la resistencia a la insulina y/o el síndrome metabólico hasta la diabetes mellitus de tipo 2 en un paciente que lo necesite, que se caracteriza porque se administra una composición farmacéutica que comprende un derivado de pirazol-O-glucósido seleccionado del grupo de compuestos (1) a (29), o su profármaco, o su sal farmacéuticamente aceptable, definido como en la reivindicación 1.

4. Un método para prevenir, frenar la progresión, retrasar o tratar un trastorno o afección seleccionado del grupo que consiste en complicaciones de la diabetes mellitus, como cataratas y enfermedades micro- y macrovasculares, como nefropatía, retinopatía, neuropatía, isquemia de tejidos, arteriosclerosis, infarto de miocardio, accidentes cerebrovasculares y enfermedad oclusiva arterial periférica, en un paciente que lo necesite, que se caracteriza porque se administra una composición farmacéutica que comprende un derivado de pirazol-O-glucósido seleccionado del grupo de compuestos (1) a (29), o su profármaco, o su sal farmacéuticamente aceptable, definido como en la reivindicación 1.

5. Un método para reducir el peso o prevenir un aumento de peso o facilitar una reducción de peso en un paciente que lo necesite, que se caracteriza porque se administra una composición farmacéutica que comprende un derivado de pirazol-O-glucósido seleccionado del grupo de compuestos (1) a (29), o su profármaco, o su sal farmacéuticamente aceptable, definido como en la reivindicación 1.

6. Un método para prevenir, frenar, retrasar o tratar la degeneración de células beta pancreáticas y/o la disminución de la funcionalidad de las células beta pancreáticas y/o para mejorar y/o restablecer la funcionalidad de las células beta pancreáticas y/o restablecer la funcionalidad de la secreción de insulina pancreática en un paciente que lo necesite, que se caracteriza porque se administra una composición

farmacéutica que comprende un derivado de pirazol-O-glucósido seleccionado del grupo de compuestos (1) a (29), o su profármaco, o su sal farmacéuticamente aceptable, definido como en la reivindicación 1.

5 7. Un método para mantener y/o mejorar la sensibilidad a la insulina y/o para tratar o prevenir la hiperinsulinemia y/o la resistencia a la insulina en un paciente que lo necesite, que se caracteriza porque se administra una composición farmacéutica que comprende un derivado de pirazol-O-glucósido seleccionado del grupo de compuestos (1) a (29), o su profármaco, o su sal farmacéuticamente aceptable, definido como en la reivindicación 1.

10 8. Un método según una o más de las reivindicaciones 1 a 7, que se caracteriza porque una composición farmacéutica que comprende una cantidad de 1 mg a 1000 mg de un derivado de pirazol-O-glucósido seleccionado del grupo de compuestos (1) a (29), o su profármaco, o su sal farmacéuticamente aceptable, definido como en la reivindicación 1, se administra diariamente con respecto a un
15 paciente adulto.

9. Un método según uno o más de las reivindicaciones 1 a 8, en el que el paciente es un individuo diagnosticado con uno o más trastornos seleccionados del grupo que consiste en sobrepeso, obesidad, obesidad visceral y obesidad abdominal.

20 10. Un método según una o más de las reivindicaciones 1 a 8, en el que el paciente es un individuo que muestra uno, dos o más de los siguientes trastornos:

- (a) una concentración de glucosa sanguínea o de glucosa sérica en ayunas mayor que 110 mg/dl, en particular mayor que 125 mg/dl;
- (b) una concentración de glucosa plasmática posprandial igual o mayor que 140 mg/dl;
- 25 (c) un valor de HbA1c igual o mayor que 6,5 %, en particular igual o mayor que 8,0 %.

11. Un método según una o más de las reivindicaciones 1 a 8, en el que el paciente es un individuo en el que uno, dos, tres o más de los siguientes trastornos están presentes:

- 30 (a) obesidad, obesidad visceral y/u obesidad abdominal,
- (b) nivel sanguíneo de triglicéridos ≥ 150 mg/dl,
- (c) nivel sanguíneo de colesterol HDL < 40 mg/dl en pacientes femeninos, y < 50 mg/dl en pacientes masculinos,
- (d) una presión sanguínea sistólica ≥ 130 mm Hg, y una presión sanguínea
35 diastólica ≥ 85 mm Hg,

- (e) un nivel sanguíneo de glucosa en ayunas ≥ 110 mg/dl.
12. Un método según una o más de las reivindicaciones 1 a 11, en el que el paciente es un individuo para el cual está contraindicado el tratamiento con metformina y/o tiene una intolerancia a la metformina en dosis terapéuticas.
- 5 13. Un método según una o más de las reivindicaciones 1 a 11, en el que el paciente es un individuo con un control glucémico insuficiente, a pesar de un tratamiento con uno o más fármacos antidiabéticos.
- 10 14. Un método según una o más de las reivindicaciones 1 a 13, en el que el derivado de pirazol-O-glucósido es un profármaco seleccionado del grupo de compuestos (1) a (29), como se define en la reivindicación 1, en los que el átomo de hidrógeno del grupo hidroxilo en la posición 6 del grupo β -D-glucopiranosilo está sustituido por un grupo seleccionado de (alquil C_{1-3})carbonilo, (alquil C_{1-6})oxicarbonilo, feniloxicarbonilo, benciloxicarbonilo y bencilcarbonilo, o su sal farmacéuticamente aceptable.
- 15 15. Un método según la reivindicación 14, en el que el profármaco de un derivado de pirazol-O-glucósido se selecciona del grupo de compuestos (30a) a (45a), (30b) a (45b), y (46) a (63) definidos como en la reivindicación 20 y 21, o su sal farmacéuticamente aceptable, o del grupo de compuestos (64) a (73)
- (64) 4-(3-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-metoxicarbonil- β -D-glucopiranos-1-iloxi)-1H-pirazol;
- (65) 4-(4-etilbencil)-1-isopropil-5-trifluorometil-3-(6-O-metoxicarbonil- β -D-glucopiranos-1-iloxi)-1H-pirazol;
- (66) 4-(4-bromobencil)-1-isopropil-5-trifluorometil-3-(6-O-metoxicarbonil- β -D-glucopiranos-1-iloxi)-1H-pirazol;
- (67) 4-(4-etilbencil)-1-ciclobutil-5-trifluorometil-3-(6-O-metoxicarbonil- β -D-glucopiranos-1-iloxi)-1H-pirazol;
- (68) 4-(4-etilbencil)-1-(2-fluoro-1-fluorometiletil)-5-trifluorometil-3-(6-O-metoxicarbonil- β -D-glucopiranos-1-iloxi)-1H-pirazol;
- (69) 4-(3-fluoro-4-metoxibencil)-1-isopropil-5-trifluorometil-3-(6-O-metoxicarbonil- β -D-glucopiranos-1-iloxi)-1H-pirazol;
- (70) 4-(3-fluoro-4-metilbencil)-1-isopropil-5-metil-3-(6-O-metoxicarbonil- β -D-glucopiranos-1-iloxi)-1H-pirazol;
- (71) 4-(4-isopropoxibencil)-1-isopropil-5-metil-3-(6-O-metoxicarbonil- β -D-

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glucopiranos-1-iloxi)-1H-pirazol;

(72) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-metoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;

(73) 4-(4-etilbencil)-1-isopropil-5-metil-3-(6-O-metoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;

o su sal farmacéuticamente aceptable.

16. El uso de un derivado de pirazol-O-glucósido seleccionado del grupo de compuestos (1) a (29), o su profármaco, o su sal farmacéuticamente aceptable, definido como en la reivindicación 1, para la fabricación de un medicamento para un método terapéutico según una o más de las reivindicaciones 1 a 15.

17. Un medicamento o composición farmacéutica para su uso en un método según una o más de las reivindicaciones 1 a 15, que comprende una cantidad terapéutica o profilácticamente eficaz de un derivado de pirazol-O-glucósido seleccionado del grupo de compuestos (1) a (29), o su profármaco, o su sal farmacéuticamente aceptable, definido como en la reivindicación 1.

18. Un derivado de pirazol-O-glucósido seleccionado del grupo que consiste en:

- (1) 4-(2,3-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (2) 4-(2,5-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (3) 4-(2,6-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (4) 4-(3,5-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (5) 1-ciclobutil-4-(3-fluoro-4-metilbencil)-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (6) 1-ciclopropilmetil-4-(3-fluoro-4-metilbencil)-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (7) 1-ciclobutil-4-(2-fluoro-4-metoxibencil)-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (8) 4-(3-cloro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-

pirazol;

- (9) 4-(2-cloro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (10) 4-(4-bromo-3-fluorobencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (11) 4-(2,3-difluoro-4-metilbencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (12) 4-(2-fluoro-4-metilbencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (13) 4-(3-fluoro-4-etoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (14) 4-(4-etinilbencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (15) 4-(3-fluoro-4-isopropoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (17) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-trifluorometil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (18) 4-(4-bromo-2-fluorobencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (19) 4-(2-fluoro-4-isopropoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (20) 4-(2-fluoro-4-etoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;

o su profármaco, en los que uno o más grupos hidroxilo del grupo β-D-glucopiranosilo se acilan con grupos seleccionados de (alquil C₁₋₁₈)carbonilo, (alquil C₁₋₁₈)oxicarbonilo, fenilcarbonilo, fenil-(alquil C₁₋₃)-carbonilo, feniloxicarbonilo, y fenil-(alquil C₁₋₃)oxicarbonilo, o su sal farmacéuticamente aceptable.

- 5 19. Un derivado de pirazol-O-glucósido según la reivindicación 18, que se caracteriza porque es un profármaco, en el que el átomo de hidrógeno del grupo hidroxilo en la posición 6 del grupo β-D-glucopiranosilo está sustituido por un grupo seleccionado de (alquil C₁₋₃)carbonilo, (alquil C₁₋₆)oxicarbonilo, feniloxicarbonilo, benciloxicarbonilo y bencilcarbonilo, o su sal farmacéuticamente aceptable.
- 10 20. Un derivado de pirazol-O-glucósido según la reivindicación 19 seleccionado del grupo que consiste en

- (30a) 4-(2,3-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-metoxycarbonil- β -D-glucopiranos-1-iloxi)-1H-pirazol;
- (30b) 4-(2,3-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-etoxycarbonil- β -D-glucopiranos-1-iloxi)-1H-pirazol;
- (31a) 4-(3-fluoro-4-etoxibencil)-1-isopropil-5-metil-3-(6-O-metoxycarbonil- β -D-glucopiranos-1-iloxi)-1H-pirazol;
- (31b) 4-(3-fluoro-4-etoxibencil)-1-isopropil-5-metil-3-(6-O-etoxycarbonil- β -D-glucopiranos-1-iloxi)-1H-pirazol;
- (32a) 4-(3-fluoro-4-isopropoxibencil)-1-isopropil-5-metil-3-(6-O-metoxycarbonil- β -D-glucopiranos-1-iloxi)-1H-pirazol;
- (32b) 4-(3-fluoro-4-isopropoxibencil)-1-isopropil-5-metil-3-(6-O-etoxycarbonil- β -D-glucopiranos-1-iloxi)-1H-pirazol;
- (33a) 4-(2,5-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-metoxycarbonil- β -D-glucopiranos-1-iloxi)-1H-pirazol;
- (33b) 4-(2,5-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-etoxycarbonil- β -D-glucopiranos-1-iloxi)-1H-pirazol;
- (34a) 4-(2-fluoro-4-isopropoxibencil)-1-isopropil-5-metil-3-(6-O-metoxycarbonil- β -D-glucopiranos-1-iloxi)-1H-pirazol;
- (34b) 4-(2-fluoro-4-isopropoxibencil)-1-isopropil-5-metil-3-(6-O-etoxycarbonil- β -D-glucopiranos-1-iloxi)-1H-pirazol;
- (35a) 4-(2-fluoro-4-etoxibencil)-1-isopropil-5-metil-3-(6-O-metoxycarbonil- β -D-glucopiranos-1-iloxi)-1H-pirazol;
- (35b) 4-(2-fluoro-4-etoxibencil)-1-isopropil-5-metil-3-(6-O-etoxycarbonil- β -D-glucopiranos-1-iloxi)-1H-pirazol;
- (36a) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-trifluorometil-3-(6-O-metoxycarbonil- β -D-glucopiranos-1-iloxi)-1H-pirazol;
- (36b) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-trifluorometil-3-(6-O-etoxycarbonil- β -D-glucopiranos-1-iloxi)-1H-pirazol;
- (37a) 4-(2,6-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-metoxycarbonil- β -D-glucopiranos-1-iloxi)-1H-pirazol;
- (37b) 4-(2,6-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-etoxycarbonil- β -D-glucopiranos-1-iloxi)-1H-pirazol;
- (38a) 4-(3,5-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-metoxycarbonil- β -D-glucopiranos-1-iloxi)-1H-pirazol;
- (38b) 4-(3,5-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-etoxycarbonil- β -D-

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- glucopiranos-1-iloxi)-1H-pirazol;
- (39a) 1-ciclobutil-4-(3-fluoro-4-metilbencil)-5-metil-3-(6-O-metoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (39b) 1-ciclobutil-4-(3-fluoro-4-metilbencil)-5-metil-3-(6-O-etoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (40a) 1-ciclopropilmetil-4-(3-fluoro-4-metilbencil)-5-metil-3-(6-O-metoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (40b) 1-ciclopropilmetil-4-(3-fluoro-4-metilbencil)-5-metil-3-(6-O-etoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (41a) 1-ciclobutil-4-(2-fluoro-4-metoxibencil)-5-metil-3-(6-O-metoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (41b) 1-ciclobutil-4-(2-fluoro-4-metoxibencil)-5-metil-3-(6-O-etoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (42a) 4-(4-bromo-3-fluorobencil)-1-isopropil-5-metil-3-(6-O-metoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (42b) 4-(4-bromo-3-fluorobencil)-1-isopropil-5-metil-3-(6-O-etoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (43a) 4-(2,3-difluoro-4-metilbencil)-1-isopropil-5-metil-3-(6-O-metoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (43b) 4-(2,3-difluoro-4-metilbencil)-1-isopropil-5-metil-3-(6-O-etoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (44a) 4-(4-bromo-2-fluorobencil)-1-isopropil-5-metil-3-(6-O-metoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (44b) 4-(4-bromo-2-fluorobencil)-1-isopropil-5-metil-3-(6-O-etoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (45a) 4-(2-fluoro-4-metilbencil)-1-isopropil-5-metil-3-(6-O-metoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (45b) 4-(2-fluoro-4-metilbencil)-1-isopropil-5-metil-3-(6-O-etoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;

o sus sales farmacéuticamente aceptables.

21. Un derivado de pirazol-O-glucósido seleccionado del grupo que consiste en:

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- (46) 4-(3-fluoro-4-metilbencil)-1-isopropil-5-metil-3-(6-O-etoxycarbonil-β-D-

- glucopiranos-1-iloxi)-1H-pirazol;
- (47) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-etoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (48) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-isobutiloxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (49) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-hex-1-iloxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (50) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-fenoxicarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (51) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-benciloxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (52) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-acetil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (53) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-propilcarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (54) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-isopropilcarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (55) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-bencilcarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (56) 4-(4-etilbencil)-1-isopropil-5-trifluorometil-3-(6-O-etoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (57) 4-(4-bromobencil)-1-isopropil-5-trifluorometil-3-(6-O-etoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (58) 4-(4-etilbencil)-1-ciclobutil-5-trifluorometil-3-(6-O-etoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (59) 4-(4-etilbencil)-1-(2-fluoro-1-fluorometiletil)-5-trifluorometil-3-(6-O-etoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (60) 4-(3-fluoro-4-metoxibencil)-1-isopropil-5-trifluorometil-3-(6-O-etoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (61) 4-(4-isopropoxibencil)-1-isopropil-5-metil-3-(6-O-etoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (62) 4-(3-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-(6-O-etoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;
- (63) 4-(4-etilbencil)-1-isopropil-5-metil-3-(6-O-etoxycarbonil-β-D-glucopiranos-1-iloxi)-1H-pirazol;

Resumen**MÉTODOS PARA PREVENIR Y TRATAR TRASTORNOS METABÓLICOS Y
NUEVOS DERIVADOS DE PIRAZOL-O-GLUCÓSIDO**

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La invención se refiere a métodos para prevenir o tratar trastornos metabólicos, para mejorar el control glucémico, para prevenir la progresión desde la tolerancia alterada a la glucosa, la resistencia a la insulina y/o desde el síndrome metabólico hasta la diabetes mellitus de tipo 2, para prevenir o tratar las complicaciones de la diabetes mellitus, para reducir el peso, para prevenir o tratar la degeneración de las células beta pancreáticas, para tratar la hiperinsulinemia y la resistencia a la insulina y la diabetes de tipo 1, en pacientes que lo necesiten, mediante la administración de una composición farmacéutica que comprende un pirazol-O-glucósido como se define en la reivindicación 1, o su profármaco, o su sal farmacéuticamente aceptable.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/064715

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/7056 C07H17/02 A61P3/04 A61P3/10

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)
A61K C07H

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2005/021566 A (BOEHRINGER INGELHEIM INTERNATIONAL GMBH; BOEHRINGER INGELHEIM PHARMA G) 10 March 2005 (2005-03-10)	
X	EP 1 500 403 A (AJINOMOTO CO., INC) 26 January 2005 (2005-01-26) the whole document	1-22
A	EP 1 364 957 A1 (KISSEI PHARMACEUTICAL [JP]) 26 November 2003 (2003-11-26)	

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search 13 February 2007	Date of mailing of the international search report 21/02/2007
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Bard111, Burkhart

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2006/064715

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

see additional sheet

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.:
1-22 (parts)
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.

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-20, 22 (parts)

Compounds, prodrugs, pharmaceutical compositions and medical/ pharmaceutical use of 4-benzyl-3-beta-D-glucopyranosyl pyrazole derivatives characterised by a trisubstituted 4-benzyl part, the substituents being selected from fluoro, methyl, methoxy and isopropoxy.

2. claims: 1-22 (parts)

Compounds, prodrugs, pharmaceutical compositions and medical/ pharmaceutical use of 4-benzyl-3-beta-D-glucopyranosyl pyrazole derivatives characterised by a disubstituted 4-benzyl part, the substituents being selected from fluoro and alkyl

3. claims: 1-22 (parts)

Compounds, prodrugs, pharmaceutical compositions and medical/ pharmaceutical use of 4-benzyl-3-beta-D-glucopyranosyl pyrazole derivatives characterised by a disubstituted 4-benzyl part, the substituents being selected from halogen and alkoxy.

4. claims: 1-20, 22 (parts)

Compounds, prodrugs, pharmaceutical compositions and medical/ pharmaceutical use of 4-benzyl-3-beta-D-glucopyranosyl pyrazole derivatives characterised by a disubstituted 4-benzyl part, the substituents being selected from halogen

5. claims: 1-13, 16-18, 22 (parts)

Compound, prodrugs thereof, pharmaceutical compositions and medical/ pharmaceutical use of 4-benzyl-3-beta-D-glucopyranosyl pyrazole derivatives characterised by a monosubstituted 4-benzyl part, the substituent being 4-ethinyl.

6. claims: 1-17,21, 22 (parts)

Prodrugs, pharmaceutical compositions and medical/ pharmaceutical use of 4-benzyl-3- beta-D-glucopyranosyl pyrazole derivatives characterised by a monosubstituted 4-benzyl part, the substituent being 4-ethyl.

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

7. claims: 1-17,21, 22 (parts)

Prodrugs, pharmaceutical compositions and medical/
pharmaceutical use of 4-benzyl-3- beta-D-glucopyranosyl
pyrazole derivatives characterised by a monosubstituted
4-benzyl part, the substituent being 4-bromo.

8. claims: 5, 21, 22 (parts)

Prodrugs, pharmaceutical compositions and medical/
pharmaceutical use of 4-benzyl-3- beta-D-glucopyranosyl
pyrazole prodrugs characterised by a monosubstituted
4-benzyl part, the substituent being 4-isopropoxy.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2006/064715

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2005021566	A	10-03-2005	CA 2539032 A1 EP 1660509 A2	10-03-2005 31-05-2006
EP 1500403	A	26-01-2005	AU 2003231517 A1 CA 2484306 A1 WO 03090783 A1	10-11-2003 06-11-2003 06-11-2003
EP 1364957	A1	26-11-2003	CA 2438593 A1 WO 02068439 A1 TW 593329 B US 2006142209 A1 US 2004132669 A1	06-09-2002 06-09-2002 21-06-2004 29-06-2006 08-07-2004

PATENT COOPERATION TREATY

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From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

To:

see form PCT/ISA/220

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2006/064715

International filing date (day/month/year)
27.07.2006

Priority date (day/month/year)
28.07.2005

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/7056 C07H17/02 A61P3/04 A61P3/10

Applicant
BOEHRINGER INGELHEIM INTERNATIONAL GMBH

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Bardili, Burkhardt

Telephone No. +49 89 2399-2132



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2006/064715

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in electronic form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2006/064715

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

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. 1-22 (parts); 1-15 with respect to industrial applicability

because:

- ☒ the said international application, or the said claims Nos. 1-15 relate to the following subject matter which does not require an international search (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):
- ☒ no international search report has been established for the whole application or for said claims Nos. 1-22 (parts)
- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b).
- ☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See Supplemental Box for further details

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2006/064715

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:
- ☒ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☐ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1-22 (parts)

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	
	No: Claims	1-22 (parts)
Inventive step (IS)	Yes: Claims	
	No: Claims	1-22 (parts)
Industrial applicability (IA)	Yes: Claims	16-22 (parts)
	No: Claims	

2. Citations and explanations

see separate sheet

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/EP2006/064715

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 1-15 relate to medial treatment of the human body and hence 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).

2. The applicants did not pay the additional search fees for inventions (2) and (4) - (8). Thus, this examination report considers only inventions (1) and (3).

Re Item IV

Lack of unity of invention

1. The claims relate to substituted 4-benzyl-3-beta-D-glucopyranosyl pyrazole derivatives and their medical use for the treatment of diabetes. The compounds may also be used in the treatment of prophylaxis or other metabolic diseases such as diabetic complications or obesity.

The claims recite 89 specific 4-benzyl-3-beta-D-glucopyranosyl pyrazole derivatives which comprise at least one substituent at the benzyl group and 2 further substituents at position 1 and 5 of the pyrazole ring. In addition, these compounds may be acylated at their glucose part at the 6'-hydroxy group.

Compounds displaying these structural features are disclosed in EP 1 500 403 A1. They are used for the same medical purposes as the compounds of the application owing to the fact that they prevent renal reabsorption of glucose by inhibiting SGLT2 receptors. The reference discloses the following compounds of claim 1 of the present application:

4-((2-Fluoro-4-methylphenyl)methyl)-1-isopropyl-5-methyl-1H-pyrazole-3-O-beta-D-glucopyranoside (at page 24; corresponding to compound 12 of the application)

4-((4-Ethynylphenyl)methyl)-1-isopropyl-5-methyl-1H-pyrazole-3-O-beta-D-glucopyranoside (at page 24; corresponding to compound 14 of the application)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)

International application No.

PCT/EP2006/064715

4-((2-Fluoro-4-methoxyphenyl)methyl)-1-isopropyl-5-methyl-1H-pyrazole-3-O-beta-D-glucopyranoside (at page 62; corresponding to compound 16 of the application)

4-((4-Ethylphenyl)methyl)-1-cyclobutyl-5-trifluoromethyl-1H-pyrazole-3-O-beta-D-glucopyranoside (at page 4; corresponding to compound 23 of the application)

4-((4-Ethylphenyl)methyl)-1-(2-fluoro-1-fluoromethyl-ethyl)-5-trifluoromethyl-1H-pyrazole-3-O-beta-D-glucopyranoside (at page 8; corresponding to compound 24 of the application)

4-((3-Fluoro-4-methylphenyl)methyl)-1-isopropyl-5-methyl-1H-pyrazole-3-O-beta-D-glucopyranoside (at page 62; corresponding to compound 26 of the application)

4-((3-Fluoro-4-methoxyphenyl)methyl)-1-isopropyl-5-methyl-1H-pyrazole-3-O-beta-D-glucopyranoside (at page 61; corresponding to compound 28 of the application)

4-((4-Ethylphenyl)methyl)-1-isopropyl-5-methyl-1H-pyrazole-3-O-beta-D-glucopyranoside (at page 61; corresponding to compound 29 of the application)

The reference also discloses 6'-acyl derivatives of some of these compounds, see in particular prodrugs 3a (page 3), 7 (page 8), 10-A (page 61), 12-A, 14-A, 16-A (page 62), and the 6'-methoxycarbonyl prodrug of instant compound 12 (page 24).

Since the compounds and their 6'-acyl prodrugs mentioned in the reference are used for the same purpose as in the application, the technical problem underlying the application may only be seen in the provision of further compounds and medicaments for the treatment of diabetes and the other diseases mentioned above. The application suggests 89 individual compounds for this purpose. i.e. compounds 1-29 of claim 1 and the corresponding 6'-acyl prodrugs derived from them (compounds 30-45a/b, 46-73). Given that these compounds and prodrugs do not share a common technical feature making a contribution over the prior art, the application lacks unity pursuant to Rule 13.1 PCT.

The first invention mentioned in claim 1 is based on compounds 1-4, 11, 27 and the corresponding prodrugs 30, 33, 37, 38 and 43 (see claims 19, 20). The compounds comprise a trisubstituted benzyl part the substituents of which being selected from fluoro, methyl, methoxy and isopropoxy. Although compounds comprising halogen, alkyl

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or alkoxy substituents at 4'-benzyl are mentioned in EP 1 500 403 A1, the instant group of trisubstituted benzyl glucopyranosyl pyrazole compounds is not disclosed in the citation. Hence, these compounds, the pharmaceutical compositions containing them and their use in medicine may constitute one invention.

The next invention recited in claim 1 relates to 4-benzyl-3-beta-D-glucopyranosyl pyrazole derivatives bearing two substituents at the 4-benzyl part. In view of the fact that compounds and prodrugs displaying this substitution pattern are also disclosed in the citation, the inventions relating to disubstituted benzyl glucopyranosyl pyrazole compounds are to be separated according to the nature of the 4-benzyl substituents. It follows that the second invention relates to compounds 5, 6, 12, 26 and the prodrugs 39, 40, 45, 46, 70, which are characterised by a fluoro and methyl substituent at 4-benzyl, and to pharmaceutical compositions thereof and their use in medicine.

Invention 3 is based on disubstituted benzyl pyrazole compounds comprising a halo and an alkoxy substituent at 4-benzyl, i.e. compounds 7-9, 13, 15-17, 19, 20, 25, 28 and prodrugs 31, 32, 34, 35, 36, 41, 47-55, 60, 62, 64, 69, 72.

Invention 4 is based on disubstituted benzyl pyrazole compounds comprising 2 halogen substituents at 4-benzyl, i.e. compounds 10, 18 and prodrugs 42, 44.

The next group of inventions is based on 4-benzyl-3-beta-D-glucopyranosyl pyrazole derivatives bearing one substituent at the 4-benzyl part. As compounds and prodrugs displaying this substitution pattern are also disclosed in the citation, in particular compounds comprising a 4-ethylbenzyl and 4-ethinylbenzyl moiety, this group of inventions needs to be divided into the following sub-groups:

Invention 5 relating to a 4-ethinylbenzyl glucopyranosyl pyrazole derivative, compound 14, pharmaceutical compositions thereof and its use in medicine.

Invention 6 relating to the medical and pharmaceutical use of 4-ethylbenzyl glucopyranosyl pyrazole derivatives 21, 23, 24, 29; and prodrugs 56, 58, 59, 63, 65, 67, 68, 73.

Invention 7 pertaining to the medical and pharmaceutical use of 4-bromobenzyl glucopyranosyl pyrazole derivative 22; and prodrugs 57, 66.

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Invention 8 relating to 4-isopropoxy glucopyranosyl pyrazole prodrugs no. 61, 71, and pharmaceutical compositions thereof and their use in medicine.

Invention 8 relating to 4-isopropoxy glucopyranosyl pyrazole derivatives, i.e. prodrugs no. 61, 71, and pharmaceutical compositions thereof and their use in medicine.

The inventions 1-8 are represented as follows in the claims 1-22:

- Invention 1: Claims 1-20, 22 (parts)
- Invention 2: Claims 1-22 (parts)
- Invention 3: Claims 1-22 (parts)
- Invention 4: Claims 1-20, 22 (parts)
- Invention 5: Claims 1-13, 16-18, 22 (parts)
- Invention 6: Claims 1-17, 21, 22 (parts)
- Invention 7: Claims 1-17, 21, 22 (parts)
- Invention 8: Claims 15, 21, 22 (parts).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Invention 1:

Trisubstituted 4-benzyl 3-beta-D-glucopyranosyl pyrazole compounds are not disclosed in D1/ EP 1 500 403 A1. Hence, the corresponding subject-matter of claims 1-20, and 22 (parts) is novel over the relevant prior art.

D1 discloses 4-benzyl-3-beta-D-glucopyranosyl pyrazole derivatives for the treatment of diabetes and related metabolic diseases. The instant compounds fall within the general formulae 2 and 2a defining the pharmaceutically active compounds of the citation. Therefore it was not surprising at the filing date of the application that compounds and their prodrugs as disclosed in the application may be used for the treatment of diabetes and related diseases. Thus, the subject-matter of claims 1-20, 22 (parts) does not meet the requirements of Articles 33 (3) PCT.

In the event the applicants intended to demonstrate a surprising effect of the claimed

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2A

subject-matter vis-à-vis the compounds of D1, the compounds 9-A - 14-A at page 61-62 and their prodrugs would be suitable for a comparison.

Invention 3:

D1/ EP 1 500 403 A1 discloses

4-((2-Fluoro-4-methoxyphenyl)methyl)-1-isopropyl-5-methyl-1H-pyrazole-3-O-beta-D-glucopyranoside, the 6'-methoxycarbonyl prodrug thereof, 4-((3-Fluoro-4-methoxyphenyl)methyl)-1-isopropyl-5-methyl-1H-pyrazole-3-O-beta-D-glucopyranoside, and the 6'-methoxycarbonyl prodrug thereof (pages 61-62). The compounds and prodrugs may be used in pharmaceutical compositions for the treatment of diabetes and related metabolic diseases. Hence, the subject-matter of claims 1-22 (parts) lacks novelty (Article 33 (2) PCT).

D1 discloses 4-benzyl-3-beta-D-glucopyranosyl pyrazole derivatives for the treatment of diabetes and related metabolic diseases. The instant compounds fall within the general formulae 2 and 2a defining the pharmaceutically active compounds of the citation. Therefore it was not surprising at the filing date of the application that compounds and their prodrugs as disclosed in the application may be used for the treatment of diabetes and related diseases. Thus, the subject-matter of claims 1-22 (parts) does not meet the requirements of Article 33 (3) PCT.

In the event the applicants intended to demonstrate a surprising effect of the claimed subject-matter vis-à-vis the compounds of D1, the compounds 9-A -12-A, at pages 61-62 would be suitable for a comparison.

PATENT COOPERATION TREATY

PCT/EP2006/064715

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EINGANG A Patente Biberach
05. Sep. 2007
Friedigt:

Eingang CD Patents
22. Aug. 2007

From the INTERNATIONAL BUREAU

PCT

IB	gesehen	erledigt
DK		

To:

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)HAMMANN, Heinz
c/o Boehringer Ingelheim GmbH
Binger Str. 173
55216 Ingelheim am Rhein
ALLEMAGNE

Date of mailing (day/month/year) 08 August 2007 (08.08.2007)	
Applicant's or agent's file reference P01-1906	IMPORTANT NOTIFICATION
International application No. PCT/EP2006/064715	International filing date (day/month/year) 27 July 2006 (27.07.2006)

.. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representativeName and Address
THOMAS, Leo
Georg-Schinbain-Str. 221
88400 Biberach
GermanyState of Nationality
DEState of Residence
DE

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 residenceName and Address
THOMAS, Leo
Löhnerfeldstr. 46
88400 Biberach
GermanyState of Nationality
DEState of Residence
DE

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office	☒ the designated Offices concerned
☐ the International Searching Authority	☐ the elected Offices concerned
☐ the International Preliminary Examining Authority	☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Blanc Veronique

Facsimile No. +41 22 338 82 70

e-mail Veronique.Blanc@wipo.int

Telephone No. +41 22 338 96 66

Form PC17/IB/306 (October 2005)

1/DCHPT4DO3

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 Industria y Comercio SUPERINTENDENCIA		SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DIVISION DE NUEVAS CREACIONES EXTRACTO PARA PUBLICACIÓN SOLICITUD DE PATENTE DE INVENCION PCT	
(21) N° de solicitud: 08-7939		(51) Int Cl: A61K 31/7056; A61P 3/04	
22) Fecha de solicitud: 28-01-2008		(71) Solicitante(s) BOEHRINGER INGELHIEM INTERNATIONAL GMBH	
(30) Prioridad	(31) Prioridad 05016390.6	(32) Fecha 28/07/2005	(33) País EP
		(72) Inventor(es) FRANK HIMMELSBACH Y OTROS	
		(74) Apoderado: EMILIO FERRERO	
(85)	Fecha limite inicio fase nacional: 28/02/2008		(87) Publicación internacional
(86)	Datos relativos a la presentación de la solicitud PCT		Fecha: 08/02/2007
	Fecha de presentación de la solicitud: 27/07/2006		N° publicación: WO 2007/014895 A3
	No. de solicitud PCT/EP2006/064715		
(54) Titulo: METODOS PARA PREVENIR Y TRATAR TRASTORNOS METABOLICOS Y NUEVOS DERIVADOS DE PIRAZOL-O-GLUCOSIDO			

Reivindicación(es):

1. Un método para prevenir, frenar la progresión, retrasar o tratar un trastorno metabólico seleccionado del grupo que consiste en diabetes mellitus de tipo 1, diabetes mellitus de tipo 2, tolerancia alterada a la glucosa, hiperglucemia, hiperglucemia posprandial, sobrepeso, obesidad y síndrome metabólico en un paciente que lo necesite, que se caracteriza porque una composición farmacética que comprende un derivado de pirazol-O-glucósido seleccionado del grupo de compuestos (1) a (29) que consiste en

- (1) 4-(2,3-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (2) 4-(2,5-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (3) 4-(2,6-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (4) 4-(3,5-difluoro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (5) 1-ciclobutil-4-(3-fluoro-4-metilbencil)-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (6) 1-ciclopropilmetil-4-(3-fluoro-4-metilbencil)-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (7) 1-ciclobutil-4-(2-fluoro-4-metoxibencil)-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (8) 4-(3-cloro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (9) 4-(2-cloro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (10) 4-(4-bromo-3-fluorobencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;

- (11) 4-(2,3-difluoro-4-metilbencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (12) 4-(2-fluoro-4-metilbencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (13) 4-(3-fluoro-4-etoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (14) 4-(4-etilbencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (15) 4-(3-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (16) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (17) 4-(2-fluoro-4-metoxibencil)-1-isopropil-5-trifluorometil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (18) 4-(4-bromo-2-fluorobencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (19) 4-(2-fluoro-4-isopropoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (20) 4-(2-fluoro-4-etoxibencil)-1-isopropil-5-metil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (21) 4-(4-etilbencil)-1-isopropil-5-trifluorometil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (22) 4-(4-bromobencil)-1-isopropil-5-trifluorometil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (23) 4-(4-etilbencil)-1-ciclobutil-5-trifluorometil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (24) 4-(4-etilbencil)-1-(2-fluoro-1-fluorometil)etil-5-trifluorometil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;
- (25) 4-(3-fluoro-4-metoxibencil)-1-isopropil-5-trifluorometil-3-β-D-glucopiranos-1-iloxi-1H-pirazol;

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-007939- -00000-0000

Fecha: 2008-01-28 16:58:22 Dep. 2020 NUECREACION
Tra. 11 PATENTE IYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 220

ercio
NCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE PCT

PATENTE DE INVENCION

[X]

MODELO DE UTILIDAD []

- ◆ Indicación de que se solicita la concesión de una patente [X]
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud [X]
- ◆ Descripción de la invención [X]
- ◆ Dibujos de ser estos pertinentes []
- ◆ Comprobante de pago de las tasas establecidas [X]

COMPLETA []

INCOMPLETA []

DISEÑO INDUSTRIAL []

- ◆ Indicación de que se solicita el registro de Diseño Industrial []
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud []
- ◆ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño []
- ◆ Comprobante de pago de las tasas establecidas []

COMPLETA []

INCOMPLETA []

ESQUEMA DE TRAZADO []

- ◆ Indicación de que se solicita el registro de un Esquema de Trazado []
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud []
- ◆ Representación gráfica del esquema trazado []
- ◆ Comprobante de pago de las tasas establecidas []

COMPLETA []

INCOMPLETA []

Edgar Navarro

Firma Responsable

Fecha Enero 28/08

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
FERRERO EMILIO
Apoderado(a) y/o Representante de
BOEHRINGER INGELHEIM INTERNATIONAL GMBH

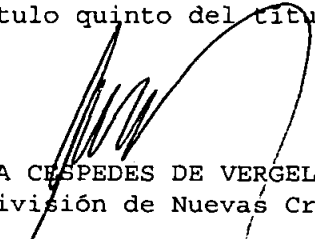
REFERENCIA	Radicación No.	8 7939
	Solicitud internacional	PCT/EP2006/064715
	Fecha inicio fase nacional	28/02/2008
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	2344

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.


ALIX CARMENZA CRESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de
fecha 15 FEB. 2008
adpall