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 Trámite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
 Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

**FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL**

1	SOLICITUD DE:			
	☒ Patente de Invención.	☐ Patente de Modelo de Utilidad.		
	☐ Capítulo I.	☒ Capítulo II.		
2	SOLICITANTE (71)	Nombre: AKZO NOBEL N.V. sociedad constituida y existente bajo las leyes de Holanda. Dirección: Velperweg 76, 6824 BM Arnhem, Holanda. Domicilio: Arnhem, Holanda.	IDENTIFICACION 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:: 217 92 11 E-mail: <u>clientes@camvp.com.</u> Domicilio: Bogotá, Colombia.	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número: <u>438.019</u> T.P. <u>31.929</u>	
4	INVENTOR (ES) (72)	Hubert Jan Jozef LOOZEN Meerhoek 602, 5403 AC Uden, Holanda.		
5	PCT (86) Solicitud Internacional No. <u>PCT/EP01/04886</u> Fecha: <u>1 de mayo de 2001</u> Publicación Internacional No. <u>WO 02/00682 A1</u> Fecha : <u>3 de enero de 2002</u>			
6	Título (54) <u>COMPUESTOS ESTEROIDES CONDENSADOS 16,17-CARBOCICLOS</u> <u>QUE TIENEN ACTIVIDAD ESTROGENICA SELECTIVA</u>			
7	Clasificación Internacional (51) <u>C07J 053/00 ; A61K 31/565</u>			
8	Prioridad SI ☒ NO ☐	(33) País de Origen <u>EP.</u>	(32) Fecha <u>8 de junio de 2000</u>	(31) Número de Solicitud <u>00201986.7</u>

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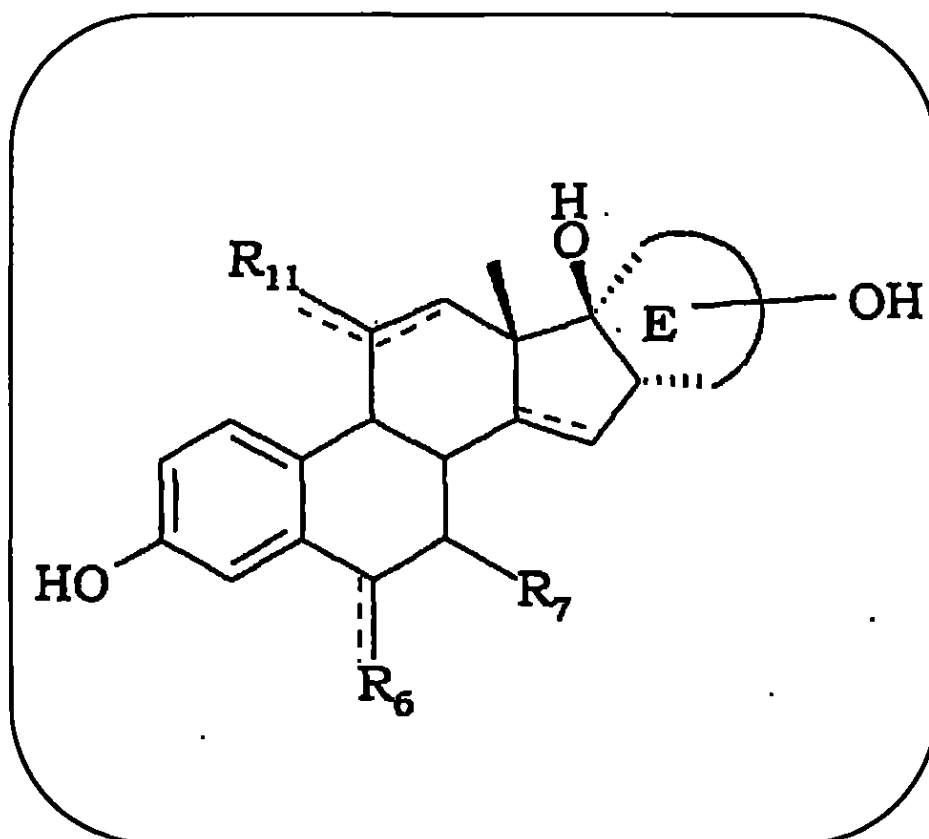
Comprobante de pago No.: 02-75,603 Fecha: 13 de noviembre de 2002

10

Απεχός:

- | | |
|-------------------------------------|---|
| ☒ | Comprobante de pago de la tasa de presentación de la solicitud por \$ 378.000.00. |
| ☐ | 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 |

11

FIGURA CARATTERISTICA:

12

Solicito la concesión de la patente,

NOMBRE: EMILIO FERRERO

FIRMA: 
C.C. 438.019 de Usaquén T.P. 31.929

JBP/mrm-ld194-

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 ATTORNEY31214
1538

I (we), the undersigned / Yo (nosotros), abajo firmado (s)

AKZO NOBEL N.V.

of/domiciliado (s) en Velperweg 76, 6824

BM Arnhem, THE NETHERLANDS

por el presente nombramos a EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 y GERMAN CAVELIER, tpa. 832, 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, 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 primer 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 EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 and GERMAN CAVELIER, tpa. 832, 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, especially those administrative, administrative contencioso-administrative, and judicial, before Arbitration Court, in all matters relating to 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 those rights; b) Actions of unfair competition, protection of the consumer, oppositions or observations, administrative and judicial cancellation, nullity, infringement, grant of licenses, action for writ mandamus, the protection of trade secrets, and in general the civil, penal, and administrative suits relating to those rights; actions and suits instituted by me (us) or against me (us). And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

Given and signed this / Dado y firmado hoy 6 AUG 1998

F.G.M. Hermans

in/en Director Patents Pharma

Signature

AKZO NOBEL N.V.

E.H. Reerink

Deputy Director

Legal Affairs

CAVELIER ABOGADOS
WPPODERE-179 (MINUTA N° 12.1.1.2.5)

TRADUCCION No. 18.11/98
MARIA ELVIRA MARRERO
Traductora e Intérprete Oficial
Inglés - Español - Inglés
Res. No. 20/9 Min. Justicia

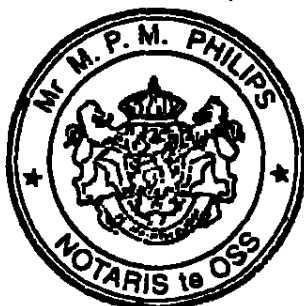
LEGALIZACION

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 darlo. 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, (2) that it is in accordance with its 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).

Seen for legalization of the signatures of Mr. F.G.M. Hermans and Mr. E.H. Reerink by me, Mr. Martinus Petrus Maria Philips, notary public at Oss, the Netherlands, on this 26th day of August 1998.



TRADUCCION No. 18/1/98
MARIA ELVIRA MARTEL
Traductora e Interprete Oficial
Inglés - Español - Inglés
Res. No. 2879 Min. Justicia

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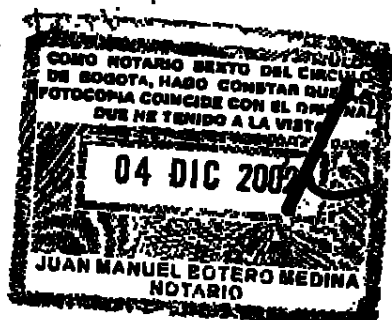


CHAMBER OF COMMERCE AND INDUSTRY
FOR OOST-BRABANT (NETHERLANDS)
EXCLUSIVE PLACE FOR LEGALIZATION OF
THE SIGNATURE(S)

27 AUG 1998

KAMERVAN NOOTDOPPE
OOST-BRABANT
's-HERTOGENBOSCH

J. Schellekens



Gezien voor legalisatie van de handtekening van de heer J. Schellekens

's-Gravenhage,

9 SEP 1998



De Minister van
Buitenlandse Zaken
voordeze,

Leges f 20,= H.H. van POORTEN

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.



CONSULADO DE COL MBIA

COLD 11214-201-001-2

El suscrito Cónsul de Colombia en La Haya, Holanda,
vistos los documentos presentados por los interesados,

CERTIFICA:

Que el Señor Martinus Petrus Maria PHILIPS, quien como Notario Público de Oss, Países Bajos, autenticó las firmas de los signatarios del poder precedente, ejercía en la fecha las funciones indicadas, y su firma corresponde a la registrada en este Consulado.

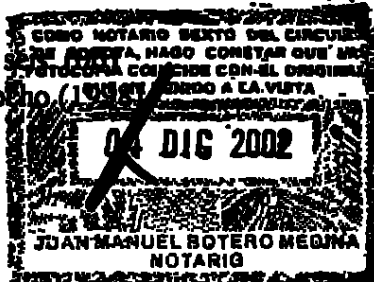
Que la Compañía AKZO NOBEL N.V. es una Sociedad constituida de acuerdo con las leyes de los Países Bajos, cumple su objeto conforme a las mismas y se halla registrada en la Cámara de Comercio y Fábricas de Centraal Gelderland, Arnhem, bajo el número 09007809;

Que los Señores Franciscus Guilielmus Maria HERMANS y Engbert Harmen REERINK, signatarios del presente documento, quienes en su carácter de Apoderados de la Empresa AKZO NOBEL N.V., conjuntamente tienen facultad para ello, y cuyas firmas fueron autenticadas ante el Notario Público de Oss, Señor Martinus Petrus Maria PHILIPS, son los representantes legales de la citada Empresa en este País.

El Cónsul de Colombia en La Haya, Países Bajos, no asume responsabilidad alguna por el contenido del documento.

Esta certificación se expide en La Haya, Países Bajos, a los siete días del mes de Noviembre de mil novecientos noventa y ocho (1998).

Impuesto de Timbre US\$ 6.00.
Derechos Consulares US\$ 100.00
Costo Total Pagado US\$ 106.00



Certificación No. 206

Jose Ignacio Villegas Cortes
JOSE IGNACIO VILLEGAS CORTES
CONSUL DE COLOMBIA
LA HAYA

TRADUCCION No. 18.11/98
MARIA ELVIRA MARTELO
Traductora e Interprete Oficial
Inglés - Español - Inglés
Res. No. 2879 Min. Justicia

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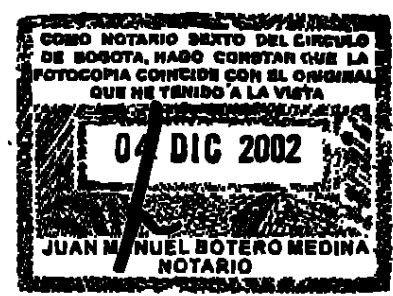
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JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

MINISTERIO DE RELACIONES
EXTERIORES

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CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

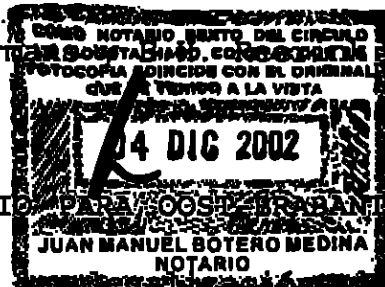


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TRADUCCIÓN OFICIAL No. 18.11/98 preparada por María Elvira Martelo, Traductora Oficial debidamente aprobada por el Ministerio de Justicia de Colombia por Resolución 2879 de 1995 y reconocida por el Ministerio de Relaciones Exteriores.

(A continuación se traducen los sellos y legalizaciones de un documento escrito en inglés y español, por el cual AKZO NOBEL N.V. otorga poder a EMILIO FERRERO, GONZALO PERDOMO, LUZ CLEMENCIA DE PAEZ Y GERMAN CAVELIER). Dado y firmado el 6 de agosto de 1998. (Firma ilegible) F.G.M. Hermans, Director de Patentes Farmacéuticas. (Firma ilegible) E.H. Reerink, Subdirector de Asuntos Jurídicos. (Sello Corporativo) AKZO NOBEL N.V.

(Al dorso) Visto por mí, Sr. Martinus Petrus Maria Philips, notario público en Oss, Países Bajos, hoy 26 de agosto de 1998, para legalización de las firmas de F.G.M. Hermans y (Firma ilegible).



(Legalización) CAMARA DE INDUSTRIA Y COMERCIO (PAÍSES BAJOS). Visto exclusivamente para la(s) firma(s) que antecede(n). Agosto 27 de 1998. (Firma ilegible) J. Schellenkens.

(Sello en holandés).

(En español) Certificación de las firmas que anteceden y de la existencia legal de AKZO NOBEL N.V. expedida por el Consulado de Colombia en La Haya el día 6 de noviembre de 1998, bajo el No.

206.. Firmado JOSE IGNACIO VILLEGAS CORTES, Cónsul de Colombia, La Haya. Pagado impuesto de timbre.

(Al dorso) Legalización de la firma que antecede expedida por el MINISTERIO DE RELACIONES EXTERIORES bajo el No. 300803 del 19 de NOVIEMBRE de 1998, firmado por el Jefe de Legalizaciones.

Es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.

COLO 11214-801-001-3

Id. 6

Nov. 20/98

Maria E. Marto
TRADUCCION No. 15.11.98
MARIA ELVIRA MARTELO
Traductora e Interprete Oficial
Inglés - Español - Inglés
Res. No. 2879 Min. Justicia

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENDIDO A LA VISTA
04 DIC 2002
JUAN MANUEL BOTERO MEDINA
NOTARIO

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE BOGOTA, HAGO CONSTAR QUE LOS ANTERIORES FIRMAS FUESTA(S) POR
[Signature]
IDENTIFICADOS CON C.C. No.(s)
ES(SON) AUTENTICAS(S)
SANTAFE DE BOGOTA, 23 NOV. 1998

BOGOTA D.C.
Circulo Sexto

MINISTERIO DE RELACIONES EXTERIORES
198457
[Signature]
CUYA FIRMA APARECE EN EL DOCUMENTO DESEMPENA LAS FUNCIONES INDICADAS

NO SE ASUME RESPONSABILIDAD DEL TEXTO
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JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

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

(19) World Intellectual Property Organization
International Bureau



INTERNATIONAL PATENT COOPERATION TREATY (PCT)

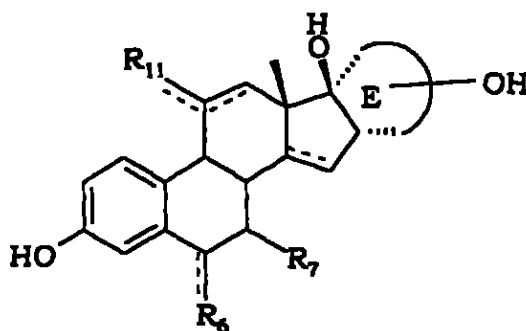
(43) International Publication Date
3 January 2002 (03.01.2002)

PCT

(10) International Publication Number
WO 02/00682 A1

- (51) International Patent Classification: C07J 53/00, A61K 31/565, A61P 5/30, 5/36 (74) Agent: KRAAK, Hajo; P.O. Box 20, NL-5340 BH Oss (NL).
- (21) International Application Number: PCT/EP01/04868 (81) Designated States (national): AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CO, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA.
- (22) International Filing Date: 1 May 2001 (01.05.2001)
- (25) Filing Language: English
- (26) Publication Language: English (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- (30) Priority Data: 00201986.7 6 June 2000 (06.06.2000) EP
- (71) Applicant (for all designated States except US): AKZO NOBEL N.V. [NL/NL]; Velperweg 76, NL-6824 BM Arnhem (NL).
- (72) Inventor; and
- (75) Inventor/Applicant (for US only): LOOZEN, Hubert, Jan, Jozef [NL/NL]; Meijrhoek 602, NL-5403 AC Uden (NL).
- Published:
— with international search report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: 16, 17-CARBOCYCLIC CONDENSED STEROID COMPOUNDS HAVING SELECTIVE ESTROGENIC ACTIVITY



(1)

(57) Abstract: The invention discloses a steroid compound having the formula (1), wherein dotted bonds represent optional double bonds; R_6 is H, $=CH_2$, or $-CH_3$, or $-CH_2-CH_3$; R_7 is H, C_{1-4} alkyl, C_{2-5} alkenyl or C_{2-5} alkynyl, wherein the alkyl, alkenyl or alkynyl group may be substituted with 1 to 3 halogen atoms independently chosen from the group of fluorine or chlorine atoms; R_{11} is H, C_{1-4} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl or C_{1-4} alkylidene, wherein the alkyl, alkenyl, alkynyl or alkylidene group may be substituted with 1 to 3 halogen atoms independently chosen from the group of fluorine or chlorine atoms; E represents together with carbon atoms 16 and 17 of the steroid skeleton a four to seven-membered ring, said ring being α and in *cis*-configuration with respect to the steroid skeleton, optionally comprising one or

two endocyclic bonds; or a prodrug thereof. Such compounds can be used in therapy and for methods for selective modification of the activity of estrogen receptors.

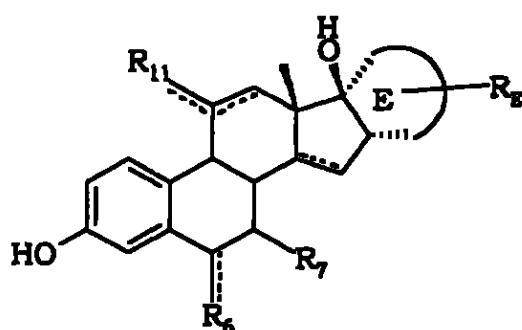
WO 02/00682 A1

16,17-CARBOCYCLIC CONDENSED STEROID COMPOUNDS HAVING SELECTIVE ESTROGENIC ACTIVITY.

The present invention relates to steroid compounds with an additional E ring connected to ring D of the steroid skeleton having estrogenic activity.

There is continued interest in new compounds with affinity for the estrogen receptor. This stems from the discovery of two distinct subtypes of receptors, denoted ER α and ER β (see Mosselman et al., FEBS Letters 392 (1996) 49-53 as well as EP -A- 0 798 378). Compounds which are selective for such subtypes of receptors make it possible to provide a more selective estrogen-receptor related treatment. Advantages can for example be obtained from the different distribution of receptor subtypes in human tissue. This enables treatments with a lower burden of estrogen-related side-effects. Examples of estrogen-related medical treatments which can benefit from selective compounds are those for contraception, for therapy of menopausal complaints, osteoporosis, and estrogen dependent tumour control.

In EP 0 869 132 estrogenic steroid compounds are described which have the formula (1):



formula 1

wherein:

dotted bonds represent optional double bonds;

R₈ is H, =CH₂, or -CH₃, or -CH₂-CH₃;

R₇ is H, C₁₋₄-alkyl, C₂₋₅ alkenyl or C₂₋₅-alkynyl, wherein the alkyl, alkenyl or alkynyl group may be substituted with 1 to 3 halogen atoms

independently chosen from the group of fluorine or chlorine atoms;

R₁₁ is H, C₁₋₄-alkyl, C₂₋₄-alkenyl, C₂₋₄-alkynyl or C₁₋₄-alkylidene, wherein the alkyl, alkenyl, alkynyl or alkylidene group may be substituted with

AMENDED SHEET

- 2 -

1 to 3 halogen atoms independently chosen from the group of fluorine or chlorine atoms;

E represents together with carbon atoms 16 and 17 of the steroid skeleton a four to seven-membered ring, said ring being α in *cis*-
5 configuration with respect to the steroid skeleton, optionally comprising one or two endocyclic bonds and substituted with R_E , which has a variety of meanings.

It was further disclosed in EP 0 869 132 that any alkyl, alkenyl, alkynyl and alkylidene group in the steroid compound having the formula (I) may
10 be branched or unbranched. If R_6 or R_{11} is connected to the steroid skeleton through a single bond, the substituted carbon atom of the steroid skeleton either comprises a hydrogen atom or is involved in a double carbon-carbon bond. Compounds may contain different centres of
chirality and can exist as enantiomers and diastereomers. Hydroxyl
15 groups may be capped with substituents such as acyl or alkyl leading to prodrugs of a compound according to formula 1.

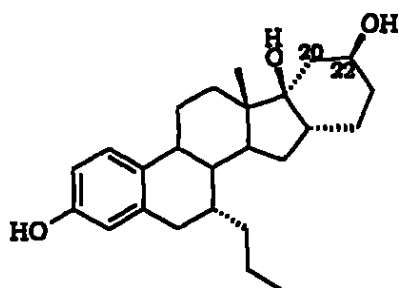
It is now found that a steroid compound having formula 1 with symbols and terms having the meanings as defined above, characterised in that
20 R_E is a β -hydroxy group, or a prodrug thereof, has, unexpectedly, a consistently better selectivity for the estrogen receptor α combined with a high estrogen α potency. Such a compound, hereafter referred to as a compound of the invention, usually is not only very weakly active on the estrogen receptor β , but in fact is generally an antagonist on the estrogen
25 receptor β , which contributes to the very high selectivity for the estrogen receptor α and furthermore enables a selective treatment based on blockade of the estrogen receptor β . The compounds of this invention include the aforementioned enantiomers and diastereomers within its scope and each of the individual (R) and (S) enantiomers, substantially
30 free, i.e. associated with less than 5%, preferably less than 2%, in particular less than 1% of the other enantiomer and mixtures of such enantiomers in any proportions including racemic mixtures containing substantially equal amounts of the two enantiomers.

35 A preferred embodiment of the invention is a steroid compound as defined previously and further characterised in that R_6 is H, R_7 is a branched or unbranched C₁₋₃-alkyl, the E-ring is a five or six-membered

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ring without double bonds having a hydroxy at position 22 in S stereoconfiguration, which configuration in other words is β with respect to the steroid skeleton according to the meaning common in steroid stereochemistry notification.

- 5 Most preferred is the compound according to formula 2, which is (7 α , 16 β , 17 α , 22S)-7-propyl-16,24-cyclo-19,21-dinorchola-1,3,5(10)-triene-3,17,22-triol, having the code name Org 41621:



10

Formula 2; Org 41621

- Compounds according to this invention enable therefore a more directed, in other words selective modification of the activity of estrogen α or β receptors in an organism.

- A prodrug is defined as being a compound which converts in the body of a recipient to a compound according to formula 1 with R_E being a β -hydroxyl group. Notably, the hydroxy groups at position 3, 17 and on the E-ring can for example be converted into ethers (alkyl*oxy) or esters such as acyl*oxy, phosphate, sulfate, sulfonate or aromatic carboxylate, whereby the carbon chain length of the groups denoted with an asterisk (*) is not considered to be sharply delimited. An acyl group is derived from a linear or branched alkane* and an aromatic carboxylate generally will comprise a phenyl, pyridinyl or pyrimidyl. The length of the alkyl and acyl groups is selected depending on the desired properties of the prodrugs, whereby the longer chained prodrugs with for example lauryl or caproyl chains are more suitable for sustained release and depot preparations. It is known that such substituents spontaneously hydrolyse or are enzymatically hydrolysed to the free hydroxyl substituents on the skeleton of the compound. Such prodrugs will have biological activity comparable to the compounds to which they are

30

converted in the body of the recipients. The active compound to which a prodrug is converted is called the parent compound. The onset of action and duration of action as well as the distribution in the body of a prodrug may differ from such properties of the parent compound.

5

Both for medical therapies as well as for physiological, medical and pharmacological experiments such selective compounds as found now are desperately needed. It is an aspect of the invention that a compound of the invention can be used for therapy by administering the compound
10 to a recipient, being human or an animal, preferably a mammal. The different distribution of α and β receptors over different tissues of an organism provides targets for more selective interference with the functioning of different tissues. It is known that species dependent, estrogen receptors α are expressed predominantly in vaginal tissue and
15 liver tissue, whereas β receptors are expressed predominantly in prostate tissue, the epithelial cell layer of rat bladder, vascular endothelial smooth muscle cells and certain brain regions, such as the basal forebrain, neocortex and hippocampus. Tissues wherein both receptors are present are for example the pituitary, hypothalamus, thymus, uterus, ovary and
20 bone.

The estrogen-receptor affinity profile of the compounds of the present invention, makes them suitable as improved estrogens or anti-estrogens under diminished estrogen-related side-effects. Thus, the invention discloses a method for selective modification of the activity of estrogen
25 receptors by bringing a compound of the invention into contact with estrogen receptors. Such a method can be a treatment of the human or animal body, but it can also be a non-medical method. The latter method can be an experimental method, such as an assay for selective compounds or an in vitro laboratory method to obtain information on
30 estrogen receptors or compounds interacting therewith. Preferably, these compounds can be used for selective estrogen-receptor α or β related contraceptive, experimental, or medical treatments, such as those for treatment or prevention of estrogen receptor related disorders, menopausal complaints, osteoporosis, cardiovascular disorders,
35 modulation of pituitary hormone regulation, benign prostate hypertrophy, estrogen dependent tumour control, colon cancer, endometriosis or central nervous system disorders. An important common characteristic of

- 5 -

these selective methods and treatments is that these comprise the bringing of a compound of the invention into contact with estrogen receptors

- 5 The invention also relates to the use of a compound according to the invention for the manufacture of a medicament for selective estrogen receptor related treatment and of a medicament for treatment of estrogen receptor α related disorders, comprising the administration to a patient of a compound according to the invention (in a suitable pharmaceutical
10 dosage form). In view of the antagonistic effect of a compound according to the invention on the estrogen receptor β the invention also provides for the manufacture of a medicament for treatment of estrogen receptor β related disorders, comprising the administration to a patient of a compound according to the invention (in a suitable pharmaceutical
15 dosage form).

Further, the invention relates to the use of a compound according to the invention in the manufacture of a medicament having contraceptive activity. Thus the invention also pertains to the medical indication of
20 contraception, i.e. a method of contraception comprising the administration to a subject, being a woman or a female animal, of a progestogen and an estrogen as is customary in the field, wherein the estrogen is a compound according to this invention (in a suitable pharmaceutical dosage form).

25 Finally the invention relates to the use of a compound according to the invention for the manufacture of a medicament having selective estrogenic activity, such a medicament being generally suitable in the area of HRT (hormone replacement therapy) having a menopausal
30 complaints relieving, in particular, an anti-osteoporose activity.

The dosage amounts of the present compounds will be of the normal order for estrogen-related compounds, e.g. of the order of 0.01 to 100 mg per administration.

35 To this end dosage units can be prepared containing amounts of a compound of the invention in the same order of magnitude as the above indicated treatment doses. Therefore, the present invention also relates to

a pharmaceutical composition comprising a compound of the invention mixed with one or more pharmaceutically acceptable auxiliaries.

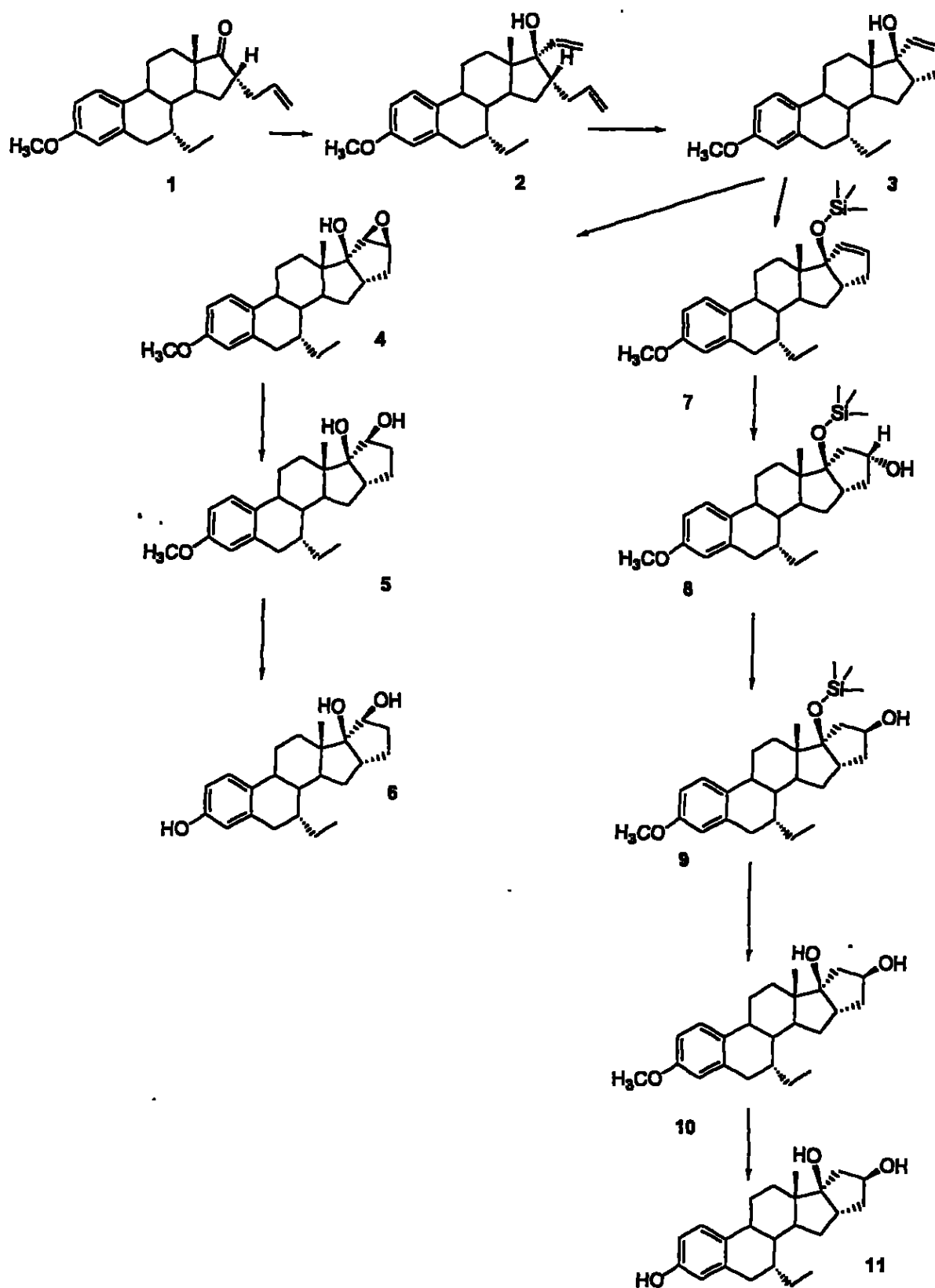
- The compounds of the invention may be produced by various methods known in the art of organic chemistry in general, and especially in the art of the chemistry of steroids. See for example: Fried, J. and Edwards, J.A., "*Organic Reactions in Steroid Chemistry*", Volumes I and II, Van Nostrand Reinhold Company, New York, 1972; and C. Djerassi, "Steroid Reactions", Holden-Day, Inc., San Francisco, 1963.
- For the synthesis of a compound according to the invention steroids with an additional 16,17 anellated ring have to be synthesised. Methods to do so have been described in EP 0 869 132. For the compounds of this invention an additional hydroxy function must be introduced on the anellated ring. For this purpose it is convenient to carry out the anellation reaction in such a way that suitably located double bonds result from the synthetic procedure, for example by using a well known olefin metathesis procedure, whereby transition metal catalysts are used which are derived from e.g. ruthenium, molybdenum, or tungsten, to close a 16 α ,17 α -bis unsaturated fragment into an unsaturated anellated 5- or 6 membered ring. The olefin ring thus synthesised is first stereoselectively epoxidized. This can be done generally with agents like peracids (preferably in a buffered medium) or catalytic systems using metal complexes in the presence of oxidizing agents (like hydrogen peroxide or t-butylhydroperoxide). In the present cases perbenzoic acid with sodiumbicarbonate buffer generally gives good results. The epoxides can be almost regioselectively reductively opened with hydride reagents to the required beta-alcohols. Hydroxy groups may be easily synthesised as well by application of a hydroboration/oxidation procedure. In cases where the α -hydroxy compounds are obtained, a Mitsunobu inversion easily leads to the β -alcohols, which are the intended ones. The hydroxy compounds can be converted into prodrugs, such as alkyl ethers, acyl esters, carbonates, sulphonates or phosphates, by reaction with the appropriate alkyl halide or acid chloride as desired.
- A pharmaceutical composition comprising one or more compounds according to the invention can be prepared with or without combination with pharmaceutically acceptable auxiliaries, such as described in the

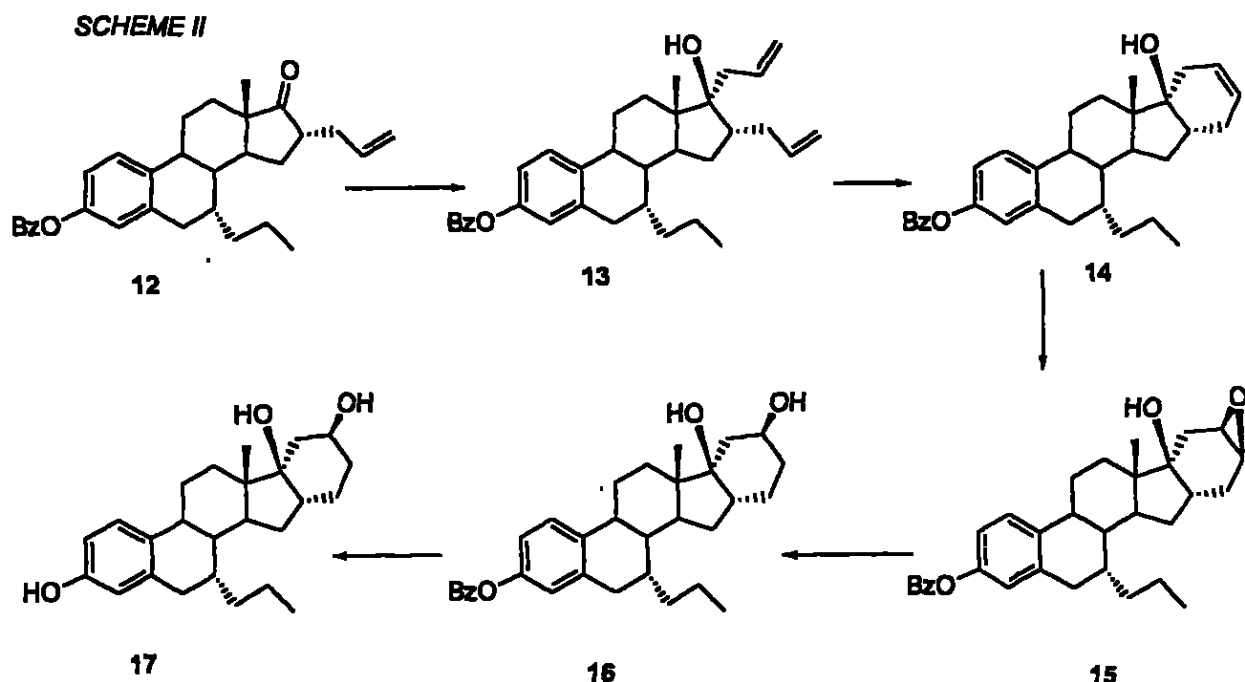
standard reference Gennaro et al., Remington's Pharmaceutical Sciences, (18th ed., Mack publishing Company, 1990, see especially Part 8: Pharmaceutical Preparations and Their Manufacture.). A mixture of one or more compounds according to the invention and one or more
5 pharmaceutically acceptable auxiliaries may be compressed into solid dosage units, such as pills or tablets, or be processed into capsules or suppositories. By means of pharmaceutically suitable liquids the compounds can also be applied as an injection preparation in the form of a solution, suspension, emulsion, or as a spray, e.g. nasal spray. The
10 compounds of the invention may also be included in an implant, a vaginal ring, a patch, a gel, and any other preparation for sustained release. For making dosage units, e.g. tablets, the use of conventional additives such as fillers or carriers, colorants, polymeric binders and the like is contemplated. In general any pharmaceutically acceptable additive
15 which does not interfere with the function of the active compounds can be used. Suitable carriers with which the compositions can be administered include lactose, starch, cellulose derivatives and the like, or mixtures thereof used in suitable amounts.

20 EXAMPLES

The routes of synthesis used in the examples are illustrated in the schemes I and II. The numbers used to identify the compounds are defined by the structural formulas in these schemes.

SCHEME I





Compound 2

To a solution of 5.65 ml of vinyltributyltin in 50 ml of dry THF was added at -50°C dropwise 12 ml of 1.6M BuLi in hexane. After stirring for an additional 0.5 hr a solution of 6.2 gr of 16 α -allyl,7 α -ethylestrone-3-O-methylether (1) in 20 ml of dry THF was added at -50°C . Upon stirring for an additional $\frac{1}{2}$ h the mixture was poured into sat. NH_4Cl and extracted with ethylacetate. Concentration of the organic phase followed by silicagel chromatography gave 4.2 g of 2 as an oil, R_f 0.47 (toluene/ethyl acetate 95/5), for 1 R_f 0.65. NMR (CDCl_3) δ 5.80 (m, 1, CH allyl), 6.07 (m, 1, CH vinyl), 0.98 (s, 3, CH_3), 0.93 (t, 3, ethyl), 3.78 (s, 3, CH_3).

Compound 3

To a solution of 4.2 g of 2 in 80 ml of methylenechloride was added 0.32 g of benzylidenetriscyclohexylphosphinoruthenium dichloride (Grubbs metathesis catalyst). After stirring for 1 hr an additional portion of 0.3 g of catalyst was added. After completion of the reaction (2 h) the mixture was concentrated and the residue purified by column chromatography, to provide 3.5 g of 3, R_f 0.29 (heptane/ethyl acetate 8/2, for 2 R_f 0.55). NMR (CDCl_3) δ 5.72 (m, CH=), 6.02 (m, 1, C=), 0.99 (s, 3, CH_3), 0.89 (t, 3, CH_3), 3.77 (OCH₃), 0.92 (m, 3, CH_3).

Compound 4

A mixture of 0.4 g of steroid 3 and 0.5 g of NaHCO₃ in 12 ml of methylenechloride was treated with 0.34 g of m-Cl-perbenzoic acid. After stirring for several hours at ambient temperature the reaction was
5 diluted with water, and treated with sodiumthiosulphate solution to destroy residual peroxide. The organic material was extracted into ethyl acetate and finally purified by chromatography, to provide 110 mg of the desired β -epoxide 4; R_f 0.50 (toluene-acetone 9/1); NMR(CDCl₃) δ 0.98 (t, 3, CH₃), 0.92 (t, 3, CH₃), 3.65 + 3.70 (2xm, epoxide CH's).

10

Compound 5

A solution of 80 mg of steroid 4 in 3 ml of THF was refluxed with 10 mg of LiAlH₄. After 2 h starting material had disappeared. The mixture was quenched by addition of 30 μ l of sat. Na₂SO₄ solution and 0.20 g of
15 Na₂SO₄, stirred for 15 min and filtered over Celite. The filtrate was concentrated and the residue passed over a short silica column, to give 55 mg of 5; R_f 0.24 (toluene-acetone 9/1); NMR(CDCl₃) δ 4.04 (m, 1, CHOH), 3.78 (s, 3, OCH₃) 2.85 (m, 2, CH₂ at C6), 0.92 (s, 3, CH₃).

Compound 6

To a solution of sodiummethanethiolate (prepared from 0.7 ml of ethanethiol and 0.27 g of a 60% NaH dispersion) in 9 ml of DMF was added 120 mg of steroid 5. The mixture was refluxed for 3 h. Then the reaction was poured into water and extracted with ethyl acetate.

25 Chromatography of the organic material provided 80 mg of 6, Mp 224-226; R_f 0.30 (toluene-acetone 8/2); NMR(CDCl₃) δ 4.00 (m, 1, CHOH), 7.12(ar H1), 6.20 (ar H2), 6.54.(ar H4).

Compound 7

30 To a solution of 2.7 g of steroid 3 in 20 ml of methylenechloride and 3 ml of pyridine, was added at 0°C 1.9 ml of trimethylsilylchloride. After stirring for 1/2 h the reaction was poured into water and extracted with ethyl acetate, to provide 3.3 g of essentially pure silyloxy derivative 7, R_f 0.8 (heptane-acetone 8/2); NMR(CDCl₃) δ 0.03 (s, 9, TMS), 5.68, 5.91 (2x
35 s, CH olefin).

Compound 8

A solution of 3.2 g of **7** in 25 ml of dry THF was treated at 0°C with a solution of 2.2 ml borane-dimethylsulfide complex in 20 ml of THF. The reaction was subsequently stirred for 2 hr at 45 °C. Excess reagent was
5 destroyed by careful addition of 4.5 ml of abs.ethanol, followed by 11 ml of 2N NaOH and 7.7 ml of 30% hydrogenperoxide . The reaction was stirred overnight, diluted with water and extracted with ethyl acetate. The crude product thus obtained was purified by column chromatography and yielded 1.7 g of the desired α -alcohol **8**. R_f 0.36 (heptane-acetone
10 8/2); NMR(CDCl₃) δ 4.42 (m, 1, CHOH), 0.12 (s, 9, TMS) , 0.79 (s, 3, CH₃).

Compound 9

A solution of 1.6 g of **8** and 1.3 g of triphenylphosphine in 60 ml of
15 toluene was treated with 0.84 g of p-nitrobenzoic acid and 0.8 ml of diethylazodicarboxylate at 0°C. After stirring for 1 h the reaction was complete. The mixture was poured onto sat.aq. NaHCO₃ solution and extracted with ethyl acetate. Chromatographic purification gave 2.9 g of β -nitrobenzoate , R_f 0.64 (heptane-acetone 8/2); NMR(CDCl₃) δ 5.34 (m, 1,
20 CHOC(O)Ar), 0.91 (s, 3, CH₃), 0.95 (t, 3, CH₃), 3.80 (s, 3, OCH₃). This material was dissolved in a mixture of 40 ml of THF-methanol(1/1 v/v) and treated with 4 ml of 2N NaOH solution. After stirring for 15 min the reaction was poured into water and the product extracted into ethyl acetate. After passing through a short silica column 1.3 g of β -alcohol **9**
25 was obtained; R_f 0.64 (heptane-acetone 8/2); NMR(CDCl₃) δ 4.31 (m, 1, CHOH).

Compound 10

A solution of 1.3 g of **9** in 30 ml of acetone was treated with 2 ml of 2N
30 HCl. After 1 h the mixture was neutralized by addition of saturated NaHCO₃ and concentrated . The residue was diluted with water and extracted with ethyl acetate, to provide 1.0 g of **10**, R_f 0.10 (heptane-acetone 8/2); NMR(CDCl₃) δ 0.90 (t, 3, CH₃) 0.95 (s, 3, CH₃), 4.48 (m, 1, CHOH).

Compound 11

To a solution of sodiummethanethiolate (prepared from 0.7 ml of ethanethiol and 0.3 g of a 60% NaH dispersion) in 9 ml of DMF was added 120 mg of steroid 10. The mixture was refluxed for 3 h. Then the
5 reaction was poured into water and extracted with ethyl acetate.

Chromatography of the organic material provided 80 mg of 11, Mp 143-145 °C (ethanol-water); R_f 0.41(toluene-acetone 7/3); NMR(CDCl₃) δ 4.45 (m, 1, CHOH), 0.93 (s, 3, CH₃) 0.90 (t, 3, CH₃), 6.62 + 7.10 (AB,2, H1,2), 6.53 (d, 1, H4).

10

Compound 13

To a solution of 29 ml of 1M allylmagnesium bromide in ether was added 80 ml of dry THF. At -50°C was added 10 gr of 7α-propyl,16α-allylestrone-3-O-benzylether 12 in 40 ml of THF. After stirring for ½ h the
15 mixture was allowed to come to room temperature and poured into 300 ml of sat aq NH₄Cl. The product was extracted with ethyl acetate and purified, by chromatography over silica gel to remove stereoisomers providing 7.2 g of the desired 16α,17α-diallyl derivative 13.

R_f 0.26 (heptane-ethylacetate 9/1); 17β-allyl isomer R_f 0.45. NMR(CDCl₃)
20 δ 0.88 (t, 3, CH₃), 0.96 (s, 3, CH₃), 6.08 (m, 1, CH allyl), 5.80 (m, 1, CH allyl), 4.95-5.20 (m, 4, 2x CH₂ allyl) 5.02 (CH₂OBz).

Compound 14

A portion of 40 mg of benzyridenetriscyclohexylphosphinoruthenium
25 dichloride (Grubbs metathesis catalyst) was added to a solution of 450 mg of 13 in 10 ml of methylenechloride. After stirring for 1 h an additional 400 mg of catalyst were added. After 2 h, the solvent was removed and replaced by 20 ml of toluene and the mixture was stirred with 5 g of basic alumina at 60°C to absorb the catalyst. After filtration
30 over Celite and washing with toluene and ethyl acetate, 400 mg of alm st pure 14 was obtained; R_f 0.34 (heptane-ethylacetate 8/2); R_f 13 0.45. NMR(CDCl₃) δ 5.02 (s, 2, CH₂O) , 5.97 (s, 2, CH=CH), 0.97 (s, 3, CH₃)

Compound 15

35 To a solution of 340 mg of 14 in 0.5 ml of methylenechloride was added 8 µl of pyridine , 0.14 ml of 30% aq H₂O₂, followed by 2 mg of methyltrioxorhenium. After stirring for 1 h the epoxidation was complete,

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leading predominantly to the desired β -epoxide as well as some α -isomer. The mixture was poured onto water and sat. $\text{Na}_2\text{S}_2\text{O}_3$ and extracted with ethylacetate. Chromatography provided 230 mg of **15** and 80 mg of the undesired α -epoxide. R_f 0.36 (toluene-ethylacetate 95/5; for reference: R_f compound **14**: 0.39). $\text{NMR}(\text{CDCl}_3)$ δ 3.31, 3.38 (m, 2, $\text{CH}(\text{O})\text{CH}$).

Compound 16

A mixture of 4.2 g of **15** and 350 mg of LiAlH_4 in 20 ml of dry THF was refluxed for 2 h. Then the mixture was cooled and subsequently treated with 1 ml of sat aq. Na_2SO_4 , 28 ml of ethyl acetate and 8 g of Na_2SO_4 . After stirring for $\frac{1}{2}$ h at ambient temperature the reaction was filtered over Celite and the filtrate concentrated and chromatographed, to provide 3.4 g of **16**, Mp 147-148°C, R_f 0.20 (toluene-ethylacetate 8/2; R_f **23** 0.55). $\text{NMR}(\text{CDCl}_3)$ δ 4.25 (broad s, 1, CHOH), 0.90 (s, 3, CH_3), 0.86 (t, 3, CH_3), 5.02 (s, 2, OCH_2Ar).

Compound 17; (=7 α , 16 β , 17 α , 22S)-7-propyl-16,24-cyclo-19,21-dinorchola-1,3,5(10)-triene-3,17,22-triol

A solution of 3.3 g of **16** in 200 ml of ethanol was hydrogenated in the presence of 300 mg of 5% Pd/C. After completion of the reaction the catalyst was filtered over Celite, and the solvent concentrated. The residue was triturated with ether, and then with water, to provide 1.7 g of **17**; Mp 146-147°C, R_f 0.53 (toluene-ethylacetate 1/1; R_f **16** 0.60). $\text{NMR}(\text{CDCl}_3)$ δ 4.26 (broad s, 1, CHOH), 7.14, 6.62 AB, 2, H_1, H_2), 6.54 (d, H_4).

Tests for estrogenic activity in vitro

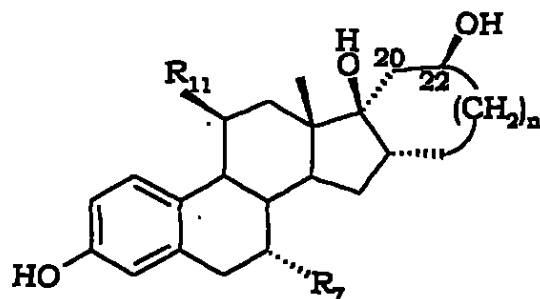
Compounds are tested for their estrogen receptor activity in a binding assay and in a transactivation assay using the human estrogen receptor α or β .

Competitive binding to cytoplasmic human estrogen receptor α or β from recombinant Chinese hamster ovary (CHO) cells is used to estimate the relative binding affinity (=RBA)(potency ratio) of a test compound as compared with (17 β)-estradiol (E_2) for estrogen receptors α or β present in the cytosol of recombinant CHO cells, stably transfected with the human estrogen receptor α (hER α) or β receptor (hER β).

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The estrogenic and antiestrogenic activity of compounds is determined in an in vitro bioassay with recombinant Chinese hamster ovary (CHO) cells stably co-transfected with the human estrogen receptor α (hER α) or β (hER β), the rat oxytocin promoter (RO) and the luciferase reporter gene (LUC). The estrogenic agonistic transactivation (potency ratio) of a test compound to stimulate the transactivation of the enzyme luciferase mediated via the estrogen receptors hER α or hER β is compared with the standard estrogen estradiol. The antiestrogenic activity (potency ratio) of a test compound to inhibit the transactivation of the enzyme luciferase mediated via the estrogen receptors hER α or hER β by the (17 β)-estradiol is compared with the standard ICI 164.384 (= (7 α ,17 β)-N-butyl-3,17-dihydroxy-N-methylestra-1,3,5(10)-triene-7-undecanamide).

Results:



Formula 3

Compound as Form. 3	R ₇	R ₁₁	6-ring (n=1) or 5-ring (n=0)	Binding-assay Er α /Er β	Trans-activation Er α /Er β	Agonist selectivity Er α /Er β
A	H	H	6-ring	8.6 / 0.3	5.5 / 0.2	27
B	CH ₃	H	6-ring	20 / 5.2	16 / <0.1	>160
C (=11)	C ₂ H ₅	H	5-ring	18 / 14	12 / <0.1	>120
D	C ₂ H ₅	H	6-ring	17 / 8.7	11.5 / <0.1	>115
E (=17 ¹⁾)	C ₃ H ₇	H	6-ring	42 / 13.9	26 / <0.1	>260
F	H	C ₃ H ₇	5-ring	16.3 / 0.4	11 / 0.2	55

¹⁾ 17 is Org 41621

Compound 17 has in the antagonist assays a selectivity ratio Er α /Er β of <0.1/67.

- 15 -

A compound of the prior art according to formula 3, but without 22-hydroxy and having R₇ α -propyl, R₁₁ hydrogen and 6-membered E-ring, which is named (7 α , 16 β , 17 α)-7-propyl-16,24-cyclo-19,21-dinorchola-1,3,5(10)-triene-3,17-diol, has a ER α /ER β ratio in the binding assay of 15/7 and in the agonist transactivation assay 0.3/<0.1.

Test for prevention of ovariectomy-induced bone loss in rats (anti-osteoporosis test).

Introduction

10 Ovariectomy of rats induces bone loss, which is due to estrogen deficiency. Administration of estrogenic compounds prevents this effect. The test is used to evaluate a compound for anti-osteoporotic activity in ovariectomised (OVX) rats. The effect on bone mass can be evaluated by peripheral Quantitative Computed Tomography (pQCT), or by quantitative
15 analysis of X-ray pictures. Plasma osteocalcin and urinary deoxypyridinoline, calcium and phosphate gives information on bone metabolism. Increase of uterine weight and decrease of body and thymus weight reflect estrogenic effect.

20 **Test animal**

Mature virgin 225-250 g female Wistar rats. Strain: Hsd/Cpd:Wu, SPF-bred by Harlan, CPB, Zeist, The Netherlands.

Experiment

25 On day 1 of the experiment the rats are weighed and distributed over the cages in order of bodyweight, whereby the rat with the smallest bodyweight is placed in the first cage and the heaviest rat in the final cage. Treatments are randomised over the rats. Sham-operation and ovariectomy are performed under ether anaesthesia.
30 After recovery from the anaesthesia, within 24 h, vehicle, reference compound or test compound is administered once or twice daily for 4 weeks. During this period the rats are weighed weekly. After 4 weeks autopsy was performed. At autopsy the rats are anaesthetised with ether and blood is collected from the abdominal aorta. Both femora, the
35 vertebrae L1L2L3L4 (optionally), uterus, thymus, liver, kidneys, adrenals, thyroid, and pituitary gland are dissected out. Measurement of bone mineral density and geometry of the right femur is performed by pQCT on

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the day of autopsy on fresh tissue. Trabecular bone mineral density of the metaphyseal part of the femur (FBMDDIS mg/cm³) is measured with a pQCT (peripheral Quantitative Computed Tomography machine; XCT 960A, Stratec, Birkenfeld, Germany).

5

Interpretation of results

Ovariectomy causes a statistically significant decrease in distal bone density and trabecular bone volume of the femur and a statistically significant increase in plasma osteocalcin and urinary deoxypyridinoline levels (P ≤ 0.05, 2 way ANOVA).

Test compounds are considered to be active when mean bone density values of the distal femur are significantly increased as compared to the ovariectomised control group. Effects of compounds on urinary deoxypyridinoline levels reflects an effect on bone resorption, effects on plasma osteocalcin levels reflects an effect on bone turnover and may help to understand the mechanism of action.

The minimal active dose (MAD) is the dose where a mean proportional difference in trabecular bone mineral density between 40 and 60% is reached.

20

References

- Wronski T.J. and Yen C.F.: The ovariectomised rat as an animal model for postmenopausal bone loss. Cells and Materials, Supp. 1 (1991): 69-76.
- Yamazaki I. and Yamaguchi H.: Characteristics of an ovariectomised osteopenic rat model. J. Bone Min. Res. 4 (1989): 12-22.
- Ederveen A.G.H. and Kloosterboer H.J.: Tibolone, a steroid with a tissue-specific hormonal profile, completely prevents ovariectomy-induced bone loss in sexually mature rats. J. Bone & Mineral Research Vol 14, pp 1963-1970, 1999.

30

Result:

Compound 17 (Org 41621) : Osteoporosis test oral 30 µg/kg.
Prior art compound (7α, 16β, 17α)-7-propyl-16,24-cyclo-19,21-dinorchola-1,3,5(10)-triene-3,17-diol: 190 µg/kg per oral.

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Test for estrogenic activity in vivo

In vivo estrogenic activity was determined by means of the Allen Doisy test, described in F.Allen, L.A.Doisy, J.Amer. Med.Assoc., 81,819-821 (1923)

5

Result:

Compound 17 (Org 41621): Allen Doisy sc 5 µg/kg , oral 30 µg/kg.

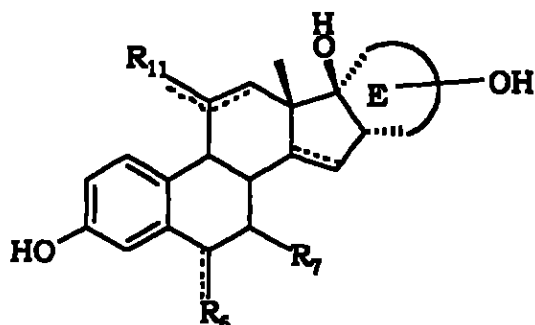
Prior art compound (7α, 16β, 17α)-7-propyl-16,24-cyclo-19,21-

dinorchola-1,3,5(10)-triene-3,17-diol: Allen Doisy sc 24 µg/kg , oral 125

10 µg/kg.

CLAIMS

1. Steroid compound having the formula (1):



formula 1

wherein:

dotted bonds represent optional double bonds;

R₆ is H, =CH₂, or -CH₃, or -CH₂-CH₃;

R₇ is H, C₁₋₄-alkyl, C₂₋₅ alkenyl or C₂₋₅-alkynyl, wherein the alkyl, alkenyl or alkynyl group may be substituted with 1 to 3 halogen atoms independently chosen from the group of fluorine or chlorine atoms;

R₁₁ is H, C₁₋₄-alkyl, C₂₋₄-alkenyl, C₂₋₄-alkynyl or C₁₋₄-alkylidene, wherein the alkyl, alkenyl, alkynyl or alkylidene group may be substituted with 1 to 3 halogen atoms independently chosen from the group of fluorine or chlorine atoms;

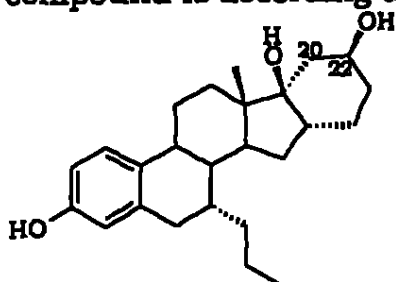
E represents together with carbon atoms 16 and 17 of the steroid skeleton a four to seven-membered ring, said ring being α in cis-configuration with respect to the steroid skeleton, optionally comprising one or two endocyclic bonds;

or a prodrug thereof.

2. Steroid compound according to claim 1, characterised in that R₆ is H, R₇ is C₁₋₃-alkyl, the E-ring is a five or six-membered ring without double bonds having a hydroxy at position 22 in S stereoconfiguration.

- 19 -

3. Steroid compound according to claim 1 or 2, characterised in that the compound is according to formula 2



formula 2,

- 5 named (7 α , 16 β , 17 α , 22S)-7-propyl-16,24-cyclo-19,21-dinorchola-1,3,5(10)-triene-3,17,22-triol,

4. A steroid compound according to any one of claims 1-3 for use in therapy.
- 10 5. A method for selective modification of the activity of estrogen receptors by bringing a compound according to any one of claim 1-3 into contact with estrogen receptors.
- 15 6. The method according to claim 5, characterised in that the method is a non-medical method
7. The method according to claim 5 or 6, characterised in that the method is a selective modification of the activity of estrogen receptors α
- 20 by bringing a compound according to any one of claims 1-3 into contact with estrogen receptors α .
8. The method according to claim 5 or 6, characterised in that the method is a selective modification of the activity of estrogen receptors β
- 25 by bringing a compound according to any one of claims 1-3 into contact with estrogen receptors β .
9. Use of the steroid compound according to any one of claim 1-3 for the manufacture of a medicament for a selective estrogen receptor related
- 30 treatment

10. The use according to claim 9, characterised in that the selective
estrogen receptor related treatment is the prevention or treatment of
peri-menopausal or post-menopausal complaints.
- 5 11. The use according to claim 9, characterised in that the estrogen
receptor related treatment is a contraceptive treatment.
12. Pharmaceutical composition comprising the steroid compound
according to any one of claims 1-3 and a pharmaceutically acceptable
10 auxilliary.

1 21 AUG. 2002
29From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

VAN WEZENBEEK, P.M.G.F.
Patent Department
P.O. Box 20
NL-5340 BH Oss
PAYS-BAS

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)Date of mailing
(day/month/year)

20.08.2002

Applicant's or agent's file reference
2000.559 WO

IMPORTANT NOTIFICATION

International application No.
PCT/EP01/04888International filing date (day/month/year)
01/05/2001Priority date (day/month/year)
06/08/2000

Applicant

AKZO NOBEL N.V. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

For the purpose of deciding whether the claimed invention is patentable or not, the elected Offices may apply criteria additional to or different from the criteria on which the international preliminary examination report is based (see Articles 27(5), 33(5)). Additional criteria may include e.g. exemptions from patentability and the requirements of enabling disclosure and of clarity and support of claims.

Name and mailing address of the IPEA/

European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized officer

Cardenas, C

Tel.+31 70 340-3370



PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

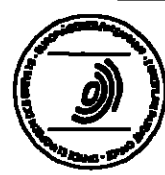
Applicant's or agent's file reference 2000.559 WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP01/04868	International filing date (day/month/year) 01/05/2001	Priority date (day/month/year) 06/06/2000
International Patent Classification (IPC) or national classification and IPC C07J53/00		
Applicant AKZO NOBEL N.V. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 9 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

 These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:
 - I ☒ Basis of the report
 - II ☐ Priority
 - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - IV ☐ Lack of unity of invention
 - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - VI ☐ Certain documents cited
 - VII ☐ Certain defects in the international application
 - VIII ☐ Certain observations on the international application

Date of submission of the demand 20/12/2001	Date of completion of this report 20.06.2002
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tlx 31 651 epo nl Fax +31 70 340 - 3016	Authorized officer Watchorn, P  Telephone No. +31 70 340 2207

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP01/04868

I. Basis of the report

1. With regard to the elements of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):
Description, pages:

3-11,14,15	as originally filed			
1,2,12,13,16,17	as received on	18/03/2002	with letter of	18/03/2002

Claims, No.:

3-12	as originally filed			
1,2	as received on	18/03/2002	with letter of	18/03/2002

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP01/04868

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under Item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-12 (in part).

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1-12 (in part) are so unclear that no meaningful opinion could be formed (*specify*):
see separate sheet

☒ the claims, or said claims Nos. 1-12 (in part) are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-12 (in part).

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 1-12

No: Claims

Inventive step (IS) Yes: Claims 1-12

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP01/04868

	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-4,6,9-12
	No:	Claims	

2. Citations and explanations
see separate sheet

III - Non-Establishment of an Opinion (Article 34(4)(b) PCT)

Claim 1 defines a generic chemical formula of 16,17-anellated estrogen derivatives and indicates that this claim also embraces "prodrugs" of these compounds. A prodrug in the context of claim 1 of the present application is any compound which is converted in vivo into a compound embraced by the generic chemical formula given in this claim (see page 3, last paragraph). Claim 1, however, gives no technical information about what chemical alterations of that chemical formula would be reversed in vivo to result in a compound according to that formula being released in vivo. In the absence of structural technical features defining what a prodrug actually is, compound claims 1-3 relate to compounds (prodrugs) defined only by a functional reference to this desirable property.

These claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such prodrug compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the prodrug compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the chemically defined generic structural formula (1) of claim 1 and claims 2 and 3 dependent thereon, and for the ether and ester-prodrugs of these compounds as specified on page 3, last paragraph of the description. The search on the first and second medicinal indications, uses and pharmaceutical compositions of claims 4-12, being characterised by the use of compounds of claims 1-3, has been limited in the same way.

Furthermore, since the above mentioned subject matter of claims 1-12 was not searched, it will not be examined as provided for in Rule 66.1(e) PCT.

V - Statement according to Article 35(2) PCT

The closest state of the art with regard to the presently claimed subject matter consists of the following document:

D1 = EP-A-869,132

The following documents are also of relevance in assessing the inventive step of the presently claimed subject matter:

D2 = US-A-3,194,821

D3 = J. Chem. Soc. (1997), pp 1179-1192

D4 = J. Med. Chem. Vol 36(20) pp 2973-2983 (1993)

[NB: The assessment of the novelty and inventive step of the presently claimed subject matter is only made in as far as the claimed subject matter is being examined (see section (III) above)]

V.IA - Industrial Applicability (Article 33(4) PCT)

For the assessment of the present claims 5, 7 and 8 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

In this regard it is noted that claim 5 relates to a method of "*selective modification of the activity of estrogen receptors*". This wording covers the method being carried out both *in vitro* and *in vivo*. This is made apparent also by the fact that dependent claim 6 states as a preferred embodiment that this is a non-therapeutic method, if claim 5 covered only non-therapeutic methods, there would be no need for dependent claim 6 specifying this as a preferred embodiment.

V.N - Novelty (Article 33(2) PCT)

The selective estrogen compounds of claim 1 have a hydroxy substituent on the 16,17- α -annelated-carbocyclic ring, which the selective estrogens disclosed in the closest state of the art (see D1, example II, compound 20, plus the 15th, 18th, 21st and 24th compounds in the table on page 19) do not have (these are unsubstituted, other derivatives disclosed in D1 have a hydrocarbon function substituent on the 16,17- α -annelated-carbocyclic ring. There are no other structural differences between the compounds of the closest state of the art disclosed in D1 and those of the application. Consequently the compounds of formula (I) of claim 1 are novel according to Article 33(2) PCT as are the compounds of dependent claims 2 and 3, the first medicinal indication of these compounds according to claim 4, the uses of these compounds according to claims 5-11 and the pharmaceutical compositions thereof according to claim 12.

V. IS - Inventive Step (Article 33(3) PCT)

The problem to be solved by the currently claimed compounds is the provision of estrogenic agents with selective activity, in particular selectivity for the estrogen α -receptor, rendering the compounds useful in particular for the treatment of osteoporosis (see page 4, paragraphs 2 and 3 and page 5, paragraph 4).

In this regard it is noted that compounds disclosed in D1 address the same problem of selective estrogen activity (see D1, page 3, lines 17-22) in particular for the treatment of osteoporosis. D1 does not indicate that the mechanism for this specificity is selective action on the estrogen α -receptor, but the therapeutic selectivity which results is the same as that achieved in the present application.

In this regard it is noted that documents D2-D4 all disclose compounds which carry hydroxy-hydrocarbyl substituents attached to position 17 α of the steroid skeleton and which display estrogenic activity (see D2, example 8 and col 1, lines 41-45; D3, page 1179, compounds 10 and 12 and page 1183, col 1, last paragraph; D4, page 2974, compound 8 and page 2975, col 2, table I). It might be taken as an evident from documents D2-D4 that hydroxy substitution of the 16 α ,17 α -annelated hydrocarbon ring of the selective estrogens of D1 would result in compounds retaining their activity and

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP01/04868

consequently the compounds of claim 1 might be seen as an obvious solution to the provision of alternative estrogenic agents useful in the treatment of osteoporosis. However, the applicant has provided comparative tests the results of which are given in the table on page 14 and page 15, lines 1-5 that the compound Org.41621 (compound E or 17 of the present invention) has a receptor specificity of $ER\alpha/ER\beta$ of at least 260, whereas the corresponding compound of the state of the art (D1) which differs from Org.41621 only in that it lacks the hydroxy substituent on the $16\alpha,17\alpha$ -annelated hydrocarbon ring, had a receptor specificity of $ER\alpha/ER\beta$ of just 3. This is a very considerable improvement in the receptor specificity of the claimed hydroxy substituted compounds of claim 1 over the corresponding non-OH substituted compounds of D1. Furthermore, none of documents D2-D4 indicate that such an improvement in $ER\alpha/ER\beta$ receptor specificity would result from the OH substitution of the $16\alpha,17\alpha$ -annelated hydrocarbon ring. Consequently, the compounds of claim 1 and claims 2 and 3 dependent thereon are an unobvious solution to the problem of providing estrogenic agents with *improved* $ER\alpha/ER\beta$ receptor specificity over those of the closest state of the art and are as such inventive according to Article 33(3) PCT, as is the first medicinal indication of these compounds according to claim 4, and as are the uses of these compounds according to claims 5-11 and the pharmaceutical compositions thereof according to claim 12.

Corrections according Rule 91 PCT

The applicant has supplied clear and detailed reasons why the errors of transcription which resulted in the consistent replacement of the Greek letter β with the letter α and the consistent replacement of the Greek letter α with the letter β . Based on the arguments given it is justified to replace each of these latinate letters with the Greek corrections mentioned above. The same applies to the replacement of the letter μ with the Greek letter μ also because there is no other measurement in the international system of units which uses a Greek letter so no other measurement other than μg (micrograms) could have been meant by this letter (which does not exist in English and the presence of which is clearly an error).

The applicant has also clarified the presence of optional double bonds in the formula of claim 1. Since the international publication of this application contains these optional double bonds clearly marked in the formula of claim 1 as published as dotted lines in

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP01/04868

the steroid structure, and given that the application was not corrected before publication, this means that the record copy of the application, sent to the International Bureau in accordance with the Rule 22 PCT and upon which the IB bases the publication, already contained this feature. Consequently its correction in the copy used in the International Preliminary Examination is allowable according to Rule 91 PCT.

Diese Unterlagen stellen die Bestätigung einer durch Telekopie (Telefax) eingereichten Anmeldung dar.

These documents represent confirmation of an application filed by facsimile.

Ces pièces constituent la confirmation d'une demande déposée par la télécopie (téléfax).

99

Datum der Übermittlung der Telekopie (Telefax):

Date of facsimile: 20-12-2001

Date de l'envoi de la télécopie (téléfax):

Name der Behörde, bei der die Telekopie (Telefax) eingereicht worden ist:

Name of authority with which facsimile was filed: EPO - MÜNCHEN

Nom de l'autorité auprès de laquelle la télécopie (téléfax) a été déposée:

The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty.

For International Preliminary Examining Authority use only	
Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference 2000.559 WO
International application No. PCT/EP01/04868	International filing date (day/month/year) 01-05-2001	(Earliest) Priority date (day/month/year) 06-06-2000
Title of invention "16, 17-CARBOCYCLIC CONDENSED STEROID COMPOUNDS HAVING SELECTIVE ESTROGENIC ACTIVITY"		
Box No. II APPLICANT(S)		
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) Akzo Nobel N.V. Velperweg 76 6824 RM ARNHEM The Netherlands		Telephone No.: 0412-666219
		Facsimile No.: 0412-650592
		Teleprinter No.:
State (i.e. country) of nationality: NL	State (i.e. country) of residence: NL	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) LOOZEN, Hubert, Jan, Jozef Meerhoek 602 5403 AC LIDEN The Netherlands		
State (i.e. country) of nationality: NL	State (i.e. country) of residence: NL	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) 		
State (i.e. country) of nationality:	State (i.e. country) of residence:	
☐ Further applicants are indicated on a continuation sheet.		

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative
and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.
☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.
☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

P.M.G.F. van Wezenbeek
P.O. Box 20
5340 BH Oss
The Netherlands

Telephone No.:

0412-666219

Facsimile No.:

0412-650592

Teleprinter No.:

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV STATEMENT CONCERNING AMENDMENTS

The applicant wishes the international Preliminary Examining Authority*

(i) ☒ to start the international preliminary examination on the basis of the international application as originally filed.

(ii) ☐ to take into account the amendments under Article 34 of
☐ the description (amendments attached).
☐ the claims (amendments attached).
☐ the drawings (amendments attached).

(iii) ☐ to take into account any amendments of the claims under Article 19 filed with the International Bureau (a copy is attached).

(iv) ☐ to disregard any amendments of the claims made under Article 19 and to consider them as reversed.

(v) ☐ to postpone the start of the international preliminary examination until the expiration of 20 months from the priority date unless that Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Box No. V ELECTION OF STATES

☒ The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)* except

(If the applicant does not wish to elect certain eligible States, the name(s) or country code(s) of those States must be indicated above.)

Box No. VI CHECK LIST

The demand is accompanied by the following documents for the purposes of international preliminary examination:

1. amendments under Article 34

description	:	sheets
claims	:	sheets
drawings	:	sheets

2. letter accompanying amendments under Article 34

: sheets

3. copy of amendments under Article 19

: sheets

4. copy of statement under Article 19

: sheets

5. other (specify):

: sheets

For International Preliminary
Examining Authority use only

received not received

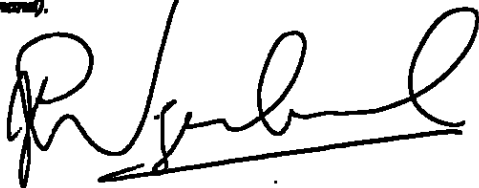
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☐ separate signed power of attorney2. ☐ copy of general power of attorney3. ☐ statement explaining lack of signature4. ☒ fee calculation sheet5. ☐ other (specify):

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).



P.M.G.F. van Wezenbeek

(AGENT)

For International Preliminary Examining Authority use

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.☐ The applicant has been informed accordingly.4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

PCT

FEE CALCULATION SHEET

Annex to the Demand for international preliminary examination

International application No. PCT/EP01/04868		For International Preliminary Examining Authority use only	
Applicant's or agent's file reference 2000.559 WO		Date stamp of the IPEA	
Applicant Akzo Nobel N.V.		COPY	
Calculation of prescribed fees			
1. Preliminary examination fee	Euro 1533,= ☒ P		
2. Handling fee (Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)	Euro 147,= ☒ H		
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box.....	Euro 1680,= TOTAL		
Mode of Payment			
☒ authorization to charge deposit account with the IPEA (see below)		☐ cash	
☐ cheque		☐ revenue stamps	
☐ postal money order		☐ coupons	
☐ bank draft		☐ other (specify):	
Deposit Account Authorization (this mode of payment may not be available at all IPEAs)			
The IPEA / EPO ☒ is hereby authorized to charge the total fees indicated above to my deposit account.			
☒ (this check-box may be marked only if the conditions for deposit accounts of the IPEA so permit) is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.			
2800 0012		20 December 2001	
Deposit Account Number		Signature <i>P. M. G. F. van Weerenbeek</i>	
Date (day/month/year)			

Form PCT/IPEA/401 (Annex) (January 1996)

See Notes to the fee calculation sheet

K3

INTERNATIONAL SEARCH REPORT

Inten	Application No
PCT/EP 01/04868	

A. CLASSIFICATION OF SUBJECT MATTER				
IPC 7	C07J53/00	A61K31/565	A61P5/30	A61P5/36
According to International Patent Classification (IPC) or to both national classification and IPC				

B. FIELDS SEARCHED				
Minimum documentation searched (classification system followed by classification symbols)				
IPC 7	C07J	A61K	A61P	
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched				

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)				
EPO-Internal, BIOSIS, CHEM ABS Data, BEILSTEIN Data				

C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 869 132 A (AKZO NOBEL NV) 7 October 1998 (1998-10-07) cited in the application example 2 page 19; table 1	1-12
Y	US 3 194 821 A (L. A. FREIBERG ET AL) 13 July 1965 (1965-07-13) column 1, line 41 - line 45; example 8 -/-	1-12

☒ Further documents are listed in the continuation of box C.		☒ Patent family members are listed in annex.	
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document relating 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. "Z" document member of the same patent family			
Date of the actual completion of the international search 23 August 2001		Date of mailing of the international search report 06/09/2001	
Name and mailing address of the ISA European Patent Office, P.B. 5518 Patentkan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 851 epo nl, Fax: (+31-70) 340-3018		Authorized officer Watchorn, P	

INTERNATIONAL SEARCH REPORT

Intern. Application No.
PCT/EP 01/04868

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	J. R. BULL ET AL: "Synthesis of 14,17-Propano analogues of estradiol" JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1., 1997, pages 1179-1192, XP002153748 CHEMICAL SOCIETY, LETCHWORTH., GB ISSN: 1470-4358 page 1179; examples 10,12 page 1183, column 1, last paragraph	1-12
Y	EL GARROUJ DRISS ET AL: "Steroidal affinity labels of the estrogen receptor: 1. 17-alpha-(Bromoacetoxy)alkyl/alkynylestrad iols." JOURNAL OF MEDICINAL CHEMISTRY, vol. 36, no. 20, 1993, pages 2973-2983, XP002153749 ISSN: 0022-2623 page 2974; example 8 page 2975, column 2; table I	1-12

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-12 (in part)

Claim 1 defines a generic chemical formula of 16,17-anellated estrogen derivatives and indicates that this claim also embraces "prodrugs" of these compounds. A prodrug in the context of claim 1 of the present application is any compound which is converted in vivo into a compound embraced by the generic chemical formula given in this claim (see page 3, last paragraph). Claim 1, however, gives no technical information about what chemical alterations of that chemical formula would be reversed in vivo to result in a compound according to that formula being released in vivo. In the absence of structural technical features defining what a prodrug actually is, compound claims 1-3 relate to compounds (prodrugs) defined only by a functional reference to this desirable property.

These claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such prodrug compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the prodrug compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the chemically defined generic structural formula (1) of claim 1 and claims 2 and 3 dependent thereon, and for the ether and ester-prodrugs of these compounds as specified on page 3, last paragraph of the description. The search on the first and second medicinal indications, uses and pharmaceutical compositions of claims 4-12, being characterised by the use of compounds of claims 1-3, has been limited in the same way.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern

Application No

PCT/EP 01/04868

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0869132 A	07-10-1998	AU 723713 B	07-09-2000
		AU 5541298 A	27-08-1998
		BR 9800718 A	29-06-1999
		CA 2229960 A	21-08-1998
		CN 1197076 A	28-10-1998
		CZ 9800505 A	16-09-1998
		HU 9800373 A	30-11-1998
		JP 10273499 A	13-10-1998
		NO 980737 A	24-08-1998
		NZ 329789 A	29-09-1999
		PL 324939 A	31-08-1998
		SG 60203 A	22-02-1999
		TR 9800282 A	21-09-1998
		TW 403736 B	01-09-2000
		US 6077873 A	20-06-2000
		ZA 9801344 A	27-08-1998
US 3194821 A	13-07-1965	NONE	

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum)

2000.559 WO

Box No. I TITLE OF INVENTION

"ANELLATED STEROID COMPOUNDS HAVING CONTRACEPTIVE AND ANTI-OSTEOPOROSIS ACTIVITY"

Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (i.e. country) of residence if no State of residence is indicated below)

Akzo Nobel N.V.

Velperweg 76

6824 BM ARNHEM

The Netherlands

☐ This person is also inventor

Telephone No.

0412-666380

Facsimile No.

0412-650592

Teleprinter No.

State (i.e. country) of nationality: NL

State (i.e. country) of residence: NL

This person is applicant
for the purposes of:☐all designated
States☒all designated States except
the United States of America☐the United States
of America only☐the States indicated in
the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (i.e. country) of residence if no State of residence is indicated below)

LOOZEN, Hubert, Jan, Jozef

Meerhoek 602

5403 AC UDEN

The Netherlands

This person is:

☐

applicant only

☒

applicant and inventor

☐inventor only (if this check-box is
marked, do not fill in below.)

State (i.e. country) of nationality: NL

State (i.e. country) of residence: NL

This person is applicant
for the purposes of:☐all designated
States☐all designated States except
the United States of America☒the United States
of America only☐the States indicated in
the Supplemental Box☐

Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

☒

agent

☐

common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

H. Kraak

P.O. Box 20

5340 BH OSS

The Netherlands

Telephone No.

0412-666382

Facsimile No.

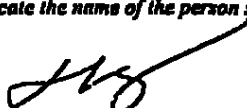
0412-650592

Teleprinter No.

☐

Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No.V	DESIGNATION OF STATES
The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):	
Regional Patent	
☒ AP	ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SI Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
☒ EA	Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
☒ EP	European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT and TR Turkey
☒ OA	OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)
National Patent (if other kind of protection or treatment desired, specify on dotted line):	
☒ AE	United Arab Emirates
☒ AG	Antigua and Barbuda
☒ AL	Albania
☐ AM	Armenia
☐ AT	Austria
☒ AU	Australia
☐ AZ	Azerbaijan
☒ BA	Bosnia and Herzegovina
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☒ CZ	Czech Republic
☐ DE	Germany
☐ DK	Denmark
☒ DM	Dominica
☒ DZ	Algeria
☒ EE	Estonia
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☐ KG	Kyrgyzstan
☒ KP	Democratic People's Republic of Korea
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☐ LS	Lesotho
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☐ LU	Luxembourg
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☒ MG	Madagascar
☒ MK	The former Yugoslav Republic of Macedonia
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☐ TZ	United Republic of Tanzania
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☐ UG	Uganda
☒ US	United States of America
☒ UZ	Uzbekistan
☒ VN	Viet Nam
☒ YU	Yugoslavia
☒ ZA	South Africa
☐ ZW	Zimbabwe
Check-box reserved for designating States which have become party to the PCT after issuance of this sheet:	
☒ CO	Colombia
Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)	

Box No. VI PRIORITY CLAIM		Further priority claims are indicated in the Supplemental Box ☐	
The priority of the following earlier application(s) is hereby claimed:			
Country <i>(in which, or for which, the application was filed)</i>	Filing Date <i>(day/month/year)</i>	Application No.	Office of filing <i>(only for regional or international application)</i>
item (1) NL	06-05-2000	00201986.7	EPO
item (2)			
item (3)			
<i>Mark the following check-box if the certified copy of the earlier application is to be issued by the Office which for the purposes of the present international application is the receiving Office (a fee may be required):</i>			
☒ The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s): 1			
Box No. VII INTERNATIONAL SEARCHING AUTHORITY			
Choice of International Searching Authority (ISA) <i>(If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):</i> ISA /EPO			
<i>Earlier search Fill in where a search (international, international-type or other) by the International Searching Authority has already been carried out or requested and the Authority is now requested to base the international search to the extent possible, on the results of that earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request</i>			
Country (or regional Office): EP		Date (day/month/year) 06-05-2000	Number: 00201986.7
Box No. VIII CHECK LIST			
This international application contains the following number of sheets: 1. request: 3 sheets 2. description: 17 sheets 3. claims: 3 sheets 4. abstract: 1 sheets 5. drawings: sheets 6. sequence listing: sheets Total : 24 sheets		This international application is accompanied by the item(s) marked below: 1. ☒ separate signed power of attorney 2. ☒ copy of general power of attorney 3. ☐ statement explaining lack of signature 4. ☐ priority document(s) identified in Box No VI as item(s): 5. ☒ fee calculation sheet 6. ☐ separate indications concerning deposited microorganisms 7. ☐ nucleotide and/or amino acid sequence listing (diskette) 8. ☒ other (specify): Request refund Letter / Copy European Search Report.	
Figure No. of the drawings (if any) should accompany the abstract when it is published.			
Box No. IX SIGNATURE OF APPLICANT OR AGENT			
<i>Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request)</i>			
 H. Kraak			

For receiving Office use only	
1. Date of actual receipt of the purported international application: 3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application: 4. Date of timely receipt of the required corrections under PCT Article 11(2): 5. International Searching Authority specified by the applicant: ISA/	2. Drawings: ☐ received ☐ not received: 6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only	
Date of receipt of the record copy by the International Bureau:	

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FEE CALCULATION SHEET

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Annex to the Request

International application No.

Applicant's or agent's
file reference **2000.559 WO**

Date stamp of the receiving Office

Applicant
Akzo Nobel N.V.

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE **EUR 102,=** **T**

2. SEARCH FEE **EUR 945,=** **S**

International search to be carried out by **EPO**
(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee
The international application contains **24** sheets.
first 30 sheets **EUR 409,=** **b₁**

remaining sheets **EUR 9,=** **EUR** **b₂**
additional amount

Add amounts entered at b₁ and b₂ and enter total at B **EUR 409,=** **B**

Designation Fees
The international application contains **61** designations

number of designation fees amount of designation fee **EUR 704,=** **D**
payable (maximum 8)

Add amounts entered at B and D and enter total at I **EUR 1113,=** **I**
(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

4. FEE FOR PRIORITY DOCUMENT **EUR 30,=** **P**

5. TOTAL FEES PAYABLE
Add amounts entered at T, S, I and P,
and enter total in the TOTAL box **EUR 2190,=**

TOTAL

☐ The designation fee is not paid at this time.

MODE OF PAYMENT

☒ authorization to charge
deposit account (see below) ☐ bank draft ☐ coupons
☐ cheque ☐ cash ☐ other (specify):
☐ postal money order ☐ revenue stamps

DEPOSIT ACCOUNT AUTHORIZATION (this mode of payment may not be available at all receiving Offices)

The RO/ **EPO** ☒ is hereby authorized to charge the total fees indicated above to my deposit account.
☒ is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.
☐ is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

2809 0012

27/04/2001

Deposit Account Number

Date (day/month/year)

Signature **H. Kraak**

Form PCT/RO/101 (Annex) (January 1996; reprint January 1998)

See Notes to the fee calculation sheet

SUPPLEMENTARY SHEET

This sheet is part of: EPA/EPO/OEB Form 1004 04.92
 concerning: General Authorisation No. 59 (rev.)
 signed in the name of: Akzo Nobel N.V.
 dated: October 4, 2000

Additional representatives:

Hermans, Franciscus G.M.
 Mestrom, Joannes Jozef Louis
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Power of Attorney
(Concerning a Given International Application)

PATENT CO-OPERATION TREATY
APPOINTMENT OF AGENT OR COMMON REPRESENTATIVE

POWER OF ATTORNEY

The undersigned applicant(s):

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Hubert, Jan, Jozef
Meerhoek 802
5403 AC UDEN
The Netherlands

hereby appoints (appoint) Mr. (Ms., Miss, Mrs.) (Name, address):

H. Kraak

P.G.W. de Weerd

F.G.M. Hermans

M. Hugenhirk

P.M.G.F. van Wezenbeek

J.J.L. Mestrom

C.M. Ogilvie-Emanuelson

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M. van Gent

All residing at:
Postbus 20
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The Netherlands

☒ as agent

☐ as common representative

to act on his (her, their) behalf before the competent International Authorities in connection with the international application on [title of the invention, applicant's or agent's file reference, if any has been indicated in the request, international application number, if already available]:

Our ref.: 2000.559 WO

Title: "ANELLATED STEROID COMPOUNDS HAVING CONTRACEPTIVE AND ANTI-OSTEOPOROSIS ACTIVITY"

filed with the [name of the Office]: EPO
as receiving Office and to make or receive payments on his (her, their) behalf.

Place: Oss Date: 24/03/2001

Signature of the applicant (where there are several applicants, each of them must sign):

H.J.J. LOOZEN

[Type the name under the (each) signature and add, in case of legal persons, an indication of the capacity in which the person signs]

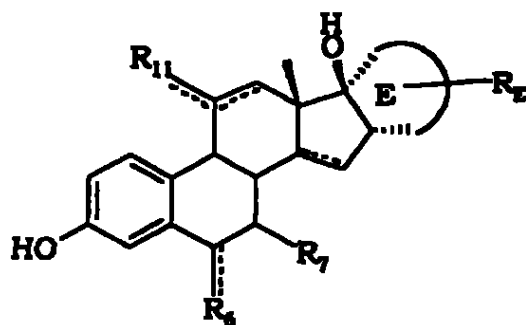
COMPUESTOS ESTEROIDES CONDENSADOS 16,17-CARBOCICLICOS QUE
TIENEN ACTIVIDAD ESTROGENICA SELECTIVA.

La presente invención se relaciona con compuestos esteroides con un anillo E adicional conectado al anillo d del esqueleto esteroide que tiene actividad estrogénica.

Existe un interés continuo en nuevos compuestos con afinidad para los receptores de estrógeno. Esto surgió a partir del descubrimiento de 2 subtipos distintos de receptores, llamados Er α y Er β (ver Mosselman et al., FEBS Letters-392 (1996) 49-53 lo mismo que la EP-A-0 798 378). Los compuestos que son selectivos para tales subtipos de receptores hacen posible suministrar un tratamiento más selectivo relacionado con receptor de estrógeno. Las ventajas pueden por ejemplo ser obtenidas a partir de la distribución diferente de los subtipos de receptor en tejidos humanos. Esto permite tratamientos con menores efectos colaterales dolorosos relacionados con el estrógeno. Ejemplos de tratamientos médicos relacionados con un estrógeno que puedan beneficiar a partir de compuestos selectivos son aquellos para la

contracepción, para la terapia de dolores menopausales,
osteoporosis y control de tumores dependientes de
estrógeno.

En la EP 0 869 132 los compuestos de esteroides
estrogenicos son descritos los cuales tienen la Fórmula
(1):



Fórmula 1

En donde:

Los enlaces en línea punteada representan enlaces dobles
opcionales;

R_6 es H, $=CH_2$, o $-CH_3$, o $-CH_2-CH_3$;

R_7 es H, alquilo C_{1-4} , alquenilo C_{2-5} o alquinilo C_{2-5} , en
donde el grupo alquilo, alquenilo o alquinilo pueden ser
sustituidos con 1 a 3 átomos halógenos escogidos

independientemente a partir del grupo de átomos de fluor o cloro;

R₁₁ es H, alquilo C₁₋₄, alquenilo C₂₋₄, alquinilo C₂₋₄ o alquilideno C₁₋₄, en donde el grupo alquilo, alquenilo, alquinilo o alquilideno se pueden sustituir con 1 a 3 átomos de halógeno independientemente escogidos del grupo de átomos de fluor o cloro;

E representa junto con los átomos de carbono 16 y 17 del esqueleto esteroide un anillo que tienen 4 a 7 miembros, dicho anillo es α en cis-configuración con respecto al esqueleto del esteroide, opcionalmente comprende 1 a 2 enlaces endocíclicos y esta sustituido con R₈, que tiene una variedad de significados.

Adicionalmente se describió en la EP 0 869 132 que cualquier alquilo, alquenilo, alquinilo o alquilideno en el compuesto esteroide que tienen la Fórmula (1) puede ser ramificado o no ramificado. Si R₈ o R₁₁ están conectados al esqueleto esteroide por medio de un enlace simple, el átomo de carbono sustituido del esqueleto esteroide comprende un átomo de hidrogeno o está involucrado en un enlace doble carbón-carbón. Los

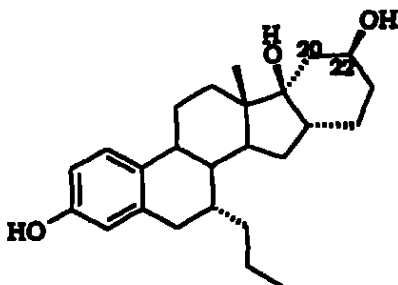
compuestos pueden contener diferentes centros de quiralidad y pueden existir como enantiomeros y diastereomeros. Los grupos hidroxilo pueden estar coronados con sustituyentes tales como acilo o alquilo que llevan la delantera hacia las prodrogas de un compuesto de acuerdo con la Fórmula 1.

Se ha encontrado ahora que un compuesto esteroide que tienen la Fórmula 1 cuyos símbolos y términos tienen los significados descritos anteriormente, caracterizado en que R_E es un grupo β -hidroxi, o una prodroga del mismo, tiene, inesperadamente, una mejor selectividad consistentemente para el receptor α de estrógeno combinado con una alta potencia α estrógeno. Tal compuesto, referido de aquí en adelante como un compuesto de la invención, usualmente no es solamente activo débilmente sobre el receptor β estrógeno, sino que de hecho es generalmente un antagonista sobre el receptor β de estrógeno, lo que contribuye a la muy alta selectividad para el receptor α de estrógeno y más aun permite un tratamiento selectivo con base en un bloqueo del receptor β de estrógeno. Los compuestos de esta invención incluyen los enantiomeros anteriormente mencionados y diastereomeros dentro de su alcance y cada

uno de los enantiomeros individuales (R) y (S), sustancialmente libres por ejemplo son asociados con menos del 5%, preferiblemente menos del 2%, en particular menos del 1% del otro enantiomero y mezclas de tales enantiomeros en cualesquier proporciones incluyendo mezclas racémicas que contienen cantidades sustancialmente iguales de los dos enantiomeros.

Una modalidad preferida de la invención es un compuesto esteroide como se definió previamente y caracterizado adicionalmente en que R_6 es H, R_7 es un alquilo C_{1-3} ramificado o no ramificado, el anillo E es un anillo con cinco o seis miembros sin enlaces dobles que tienen un hidroxil en la posición 22 en la estereo configuración S, dicha configuración en otras palabras es β con respecto al esqueleto esteroide de acuerdo con el significado común en la marcación estereoquímica de esteroides.

Más preferiblemente es el compuesto de acuerdo con la Fórmula 2, que es (7 α , 16 β , 17 α , 22S)-7-propil-16,24-ciclo-19,21-dinorcola-1,3,5 (10)-tiene-3,17,22-triol, que tiene el nombre del código Org 41621:



Fórmula 2;Org 41621

Los compuestos de acuerdo con esta invención permiten por lo tanto una modificación selectiva más directa de la actividad del estrógeno de receptores α o β en un organismo.

Una prodroga es definida como un compuesto que se convierte en el cuerpo del receptor aún compuesto de acuerdo con la Fórmula 1 con R_2 siendo un grupo β -hidroxilo. Notablemente, los grupos hidroxi en las posiciones 3,17 y sobre el anillo E pueden por ejemplo ser convertidos en éteres (alquil*oxi) o esteres tales como acil*oxi, fosfato, sulfato, sulfonato o carboxilato aromático, por lo tanto la longitud de cadena de carbón de los grupos marcados con un asterisco(*) no son considerados como delimitados muy precisamente. Un grupo acilo es derivado a partir de alcano* lineal o ramificado

y un carboxilato aromático generalmente comprende un fenilo, piridinilo, o pirimidilo. Las longitudes de los grupos alquilo y acilo se seleccionan dependiendo de las propiedades deseadas de las prodrogas, así las prodrogas con cadenas más largas con por ejemplo cadenas de laurilo o caproilo y son más adecuadas para una liberación sostenida y preparaciones de depósito. Es conocido que tales sustituyentes hidrolizan espontáneamente o son hidrolizados enzimáticamente en los sustituyentes libres de hidroxilo sobre el esqueleto del compuesto. Tales prodrogas pueden tener una actividad biológica comparable a los compuestos a los cuales ellos son convertidos en el cuerpo del receptor. El compuesto activo al cual una prodroga es convertida se llama el compuesto pariente. El establecimiento de la acción y la duración de la acción lo mismo que la distribución en el cuerpo de una prodroga puede diferir a partir de tales propiedades del compuesto pariente.

Tanto para terapias médicas lo mismo que para experimentos fisiológicos, médicos y farmacológicos tales compuestos selectivos son ahora necesarios. desesperadamente. Este es un aspecto de la invención en que un compuesto de la invención puede ser usado para

terapia administrando el compuesto a un receptor, sea un humano o un animal, preferiblemente un mamífero. La distribución diferente de los receptores α y β sobre los diferentes tejidos de un organismo suministra objetivos para una interferencia más selectiva con el funcionamiento de los diferentes tejidos. Es conocido que las especies dependientes, de receptores α estrógeno son espesadas[?] predominantemente en tejidos vaginales y en tejidos de hígado, mientras que los receptores β son expresados predominantemente en tejidos de próstata, capas de células epiteliales de vejiga de rata, células de músculo suave endotelial vascular y ciertas regiones del cerebro, tales como el cerebro anterior basal, la neocortesa y el hipocampus. Los tejidos en donde ambos receptores están presentes son por ejemplo la pituitaria, hipotálamos, el timo, el útero, el ovario y el hueso.

El perfil de afinidad estrógeno-receptor de los compuestos de la presente invención, los hace adecuados como estrógenos o antiestrogenos mejorados bajo los efectos colaterales relacionados de estrógenos disminuidos. Así, la invención describe un método para la modificación selectiva de la actividad de receptores de estrógeno poniendo un compuesto de la invención en

contacto con los receptores estrógeno. Tal método puede ser un tratamiento del cuerpo humano o de un animal. Pero también puede ser un método no médico. El último método puede ser un método experimental, tal como un ensayo para compuestos selectivos o un método de laboratorio in vitro para obtener información sobre receptores de estrógeno o compuestos que interactúan con ellos. Preferiblemente, estos compuestos pueden ser usados para contraceptivos, experimentos o tratamientos médicos relacionados con estrógeno-receptor α o β tales como aquellos para el tratamiento o la prevención de desordenes relacionados con receptor de estrógeno, dolencias menopausiales, osteoporosis, desordenes cardiovasculares, modulación de la regulación de la hormona pituitaria, hipertrofia benigna de próstata, control de tumores dependientes de estrógeno, cáncer de colon, endometriosis o desordenes del sistema nervioso central. Una característica común importante de estos métodos y tratamientos selectivos es que estos comprenden la puesta en contacto de un compuesto de la invención con receptores de estrógeno.

La invención también se relaciona con el uso de un compuesto de acuerdo con la invención con la elaboración de un medicamento para tratamiento relacionado con

receptor de estrógeno selectivo y de un medicamento para el tratamiento de desordenes relacionados con receptores α de estrógeno, que comprende la administración a un paciente de un compuesto de acuerdo con la invención (en una forma de dosis farmacéutica adecuada). En vista del efecto antagonista de un compuesto de acuerdo con la invención sobre el receptor β estrógeno la invención también suministra la elaboración de un medicamento para el tratamiento de desordenes relacionados con el receptor β de estrógeno, que comprende la administración a un paciente de un compuesto de acuerdo con la invención (en una forma de dosis farmacéutica adecuada).

Adicionalmente, la invención se relaciona con el uso de un compuesto de acuerdo con la invención en la elaboración de un medicamento que tiene actividad contraceptiva. De esta manera la invención también pertenece a la indicación medica de la contracepción, es decir un método de contracepción que comprende la administración a un sujeto, siendo este un animal mujer o femenino, de un progestógeno y un estrógeno como es costumbre en el campo, en donde el estrógeno es un compuesto de acuerdo con la invención (en una forma de dosis farmacéutica adecuada).

Finalmente la invención se relaciona con el uso de un compuesto de acuerdo con la invención para la elaboración de un medicamento que tiene actividad estrogénica selectiva, tal medicamento es generalmente adecuado en el área de HRT (terapia de reemplazo hormonal) que tiene un alivio de molestas menopáusicas, en particular, de actividad anti- osteoporosa.

Las cantidades de dosis de los presentes compuestos serán de orden normal para los compuestos relacionados con estrógeno, por ejemplo, del orden de 0,01 a 100 mg por administración.

Para este fin las unidades de dosis se pueden preparar que contengan cantidades de un compuesto de la invención en el mismo orden de magnitud que las dosis de tratamiento anteriormente indicadas. Por lo tanto, la presente invención también se relaciona con una composición farmacéutica que comprende un compuesto de la invención mezclado con uno o más auxiliares farmaceuticamente aceptables.

Los compuestos de la invención se pueden producir mediante varios métodos conocidos en la técnica de química orgánica en general, y especialmente en la técnica de química de esteroides. Ver por ejemplo: Fried, J. and Edwards, J.A., "Organic Reactions in Steroid Chemistry", volúmenes I y II, Van Nostrand Reinhold Company, New York, 1972; y C. Djerassi, "Steroid Reactions", Holden-Day, Inc., San Francisco, 1963.

Para la síntesis de un compuesto de acuerdo con la invención los esteroides con un anillo anhelado 16, 17 adicional tienen que ser sintetizados. Los métodos para hacerlo así se han descrito en la EP 0 869 132. Para los compuestos de esta invención se debe introducir una función hidroxil adicional sobre el anillo anhelado. Para este propósito es conveniente llevar a cabo la reacción de anhelación de tal forma que los dobles enlaces localizados adecuadamente resulten del procedimiento sintético, por ejemplo al utilizar un procedimiento de metatesis de olefina bien conocido, por medio del cual los catalizadores de metal de transición se utilizan los cuales se derivan de por ejemplo, rutenio, molibdeno, o tungsteno, para cerrar un fragmento insaturado 16 α , 17 α -bis en un anillo de 5 o 6 miembros anhelado y saturado.

El anillo de olefina sintetizado así es primero estéreo selectivamente epoxidizado. Esto se puede hacer generalmente con agentes como perácidos (preferiblemente en un medio amortiguado) o sistemas catalíticos utilizando complejos de metal en la presencia de agentes oxidantes (como peróxido de hidrógeno o t-butilhidroperóxido). En los presentes casos el ácido perbenzoico con amortiguador de bicarbonato de sodio generalmente da buenos resultados. Los epóxidos pueden ser casi regioselectivamente reductivamente abiertos con reactivos de hidruro a los alcoholes β requeridos. Los grupos hidroxilo pueden ser fácilmente sintetizados también mediante aplicación de un procedimiento de hidrobromación/oxidación. En los casos en donde los compuestos α -hidroxilo se obtienen, una inversión Mitsunobu fácilmente conduce a los alcoholes β , que son los pretendidos. Los compuestos hidroxilo se pueden convertir en prodrogas, tales como éteres de alquilo, ésteres de acilo, carbonatos, sulfonatos o fosfatos, mediante la reacción con el haluro de alquilo apropiado o el cloruro ácido según se desee.

Una composición farmacéutica que comprende uno o más compuestos de acuerdo con la invención se puede preparar

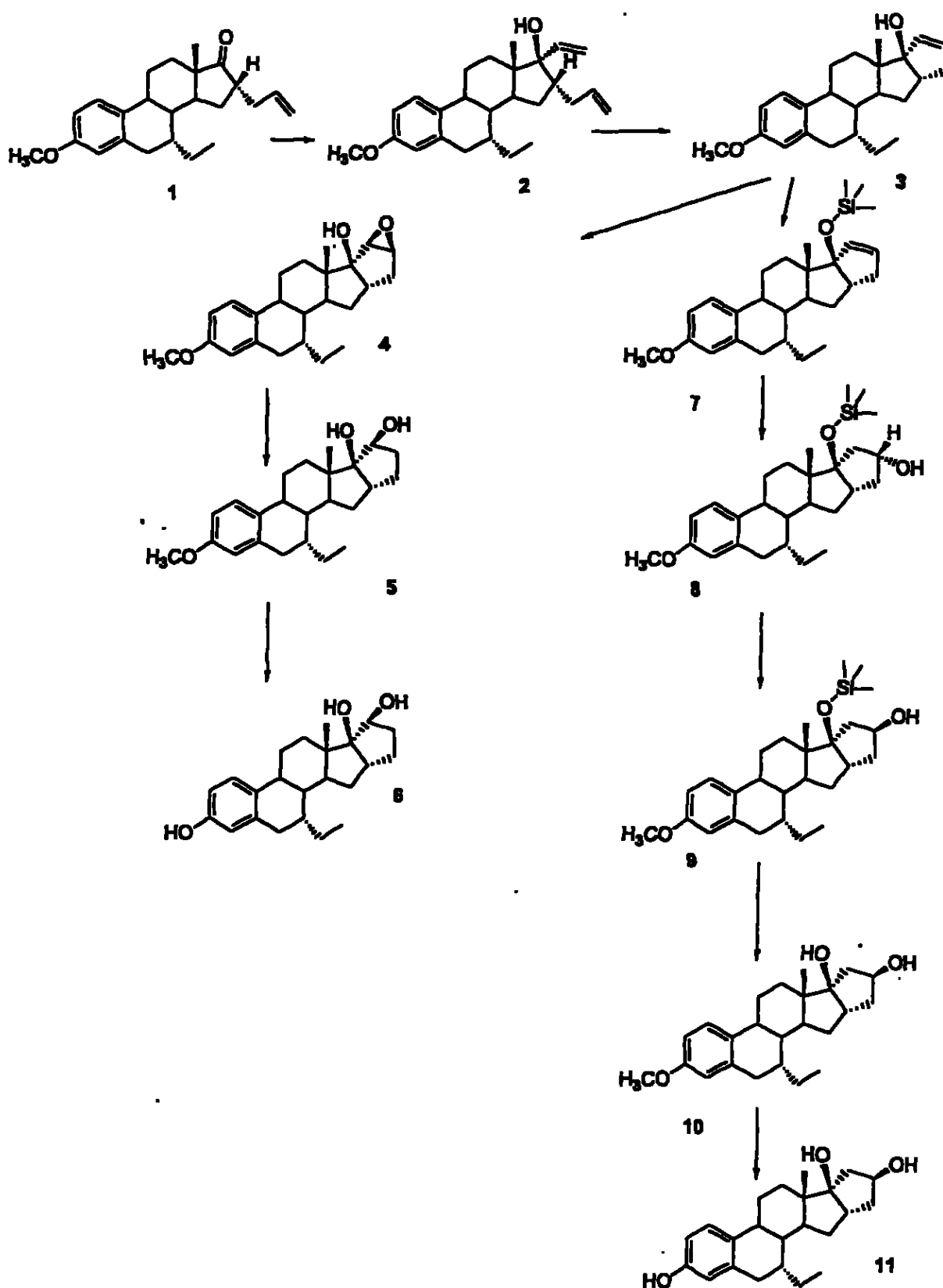
con o sin combinación con auxiliares farmaceuticamente aceptables, tales como los descritos en la referencia estándar Gennaro et al., Remmington's Pharmaceutical Science, (18th ed,. Mack publishing Company, 1990, ver especialmente parte 8: Pharmaceutical Preparations and manufacture.). Una mezcla de uno o más compuestos de acuerdo con la invención y uno o más auxiliares farmaceuticamente aceptables se puede comprimir en unidades de dosis sólidas tales como píldoras o tabletas o se puede procesar en cápsulas o supositorios. Por medio de líquidos farmaceuticamente adecuados los compuestos también se pueden aplicar como una preparación en inyección en la forma de una solución, suspensión, emulsión o un roseado, por ejemplo un roseado nasal. Los compuestos de la invención también se pueden incluir en un implante un anillo vaginal, un parche, un gel, y cualquier otra preparación para liberación sostenida. Para la elaboración de las dosis unitarias, por ejemplo, tabletas, se contempla el uso de aditivos convencionales llenadotes soportadores, colorantes, ligadores poliméricos y similares. En general cualquier aditivo farmaceuticamente aceptable que no interfiera con la función de los compuestos activos se puede utilizar. Los portadores adecuados con los cuales las composiciones se

pueden administrar incluyen derivados de lactosa, almidón, celulosa y similares o mezclas de estos utilizadas en cantidades adecuadas.

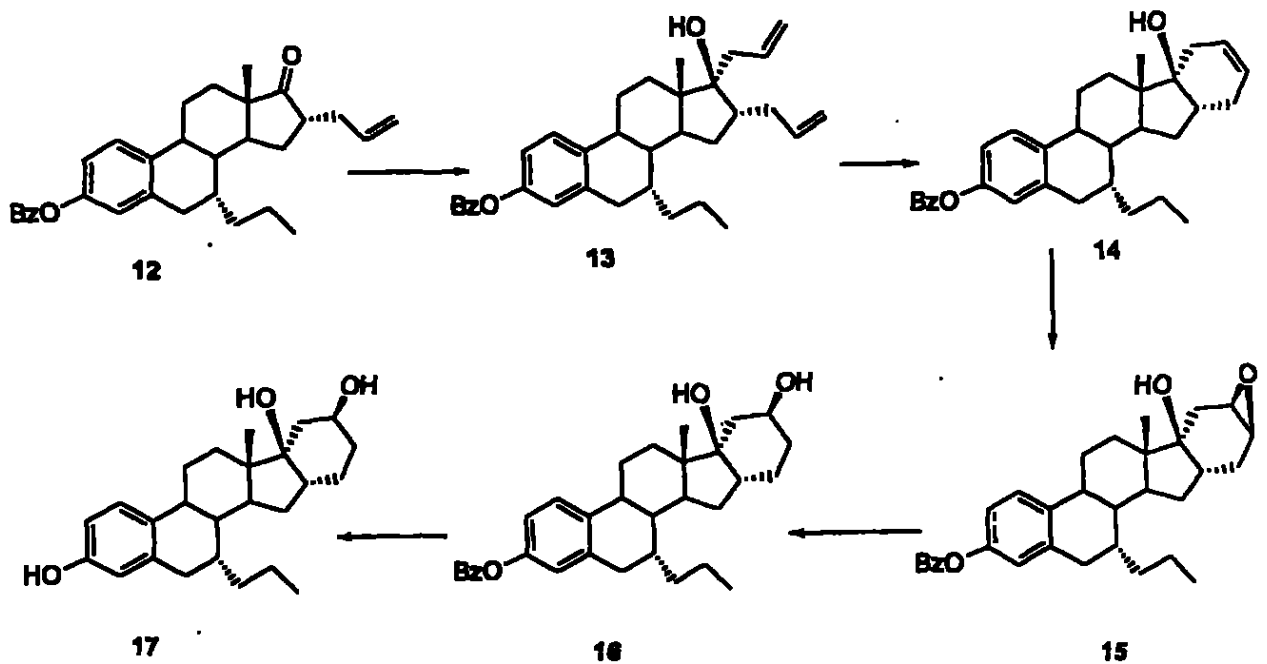
EJEMPLOS

Las rutas de síntesis utilizadas en los ejemplos se ilustran en los esquemas I y II. Los números utilizados para identificar los compuestos se definen mediante formulas estructurales en estos esquemas

ESQUEMA I



ESQUEMA II



Compuesto 2

A una solución de 5,65 ml de viniltributilestaño en 50 ml de THF seco se agregó -50°C gota a gota 12 ml de BuLi 1,6M en hexano. Después de agitar durante 0,5 h adicionales se agregó una solución de 6,2 g de 16^a-alil, 7 α -etilestrona-3-O-metileter (1) en 20 ml de THF seco a -50°C . Al agitar durante $\frac{1}{2}$ h la mezcla se vertió en NH_4Cl sat. Y se extrajo con etilacetato. La concentración de la

fase orgánica seguida por cromatografía de silicagel dio 4,2 g de 2 como un aceite.

R_f 0,47 (tolueno/etilacetato 95/5) para 1 R_f 0,65.
NMR ($CDCl_3$) δ 5,80 (m, 1, CH alilo) 6,07 (m, 1, CH vinilo) 0,98 (s, CH_3) 0,93 (t, 3, etil), 3,78 (, 3, CH_3)

Compuesto 3

A una solución de 2 en 80 ml de cloruro de metileno se agregaron 0,32 g de dicloruro de benzyldienotris(ciclohexil)fosfinorutenio (catalizador de metátesis de Grubbs). Después de agitar durante 1 h se agrego una porción adicional de 0,3 g de catalizador. Después de completar la reacción (2 h) la mezcla se concentro y el residuo se purifico mediante cromatografía de columna para suministrar 3,5 g de 3, R_f 0,29 (heptano/etilacetato 8/2, para 2 R_f 0,55). RMN ($CDCl_3$) δ 5,72 (m, CH=) 6,02 (m, 1, C=) 0,99 (s, 3, CH_3) 0,89 (t, 3, CH_3) 3,77 (OCH_3) 0,92 (m, 3, CH_3) .

Compuesto 4

Una mezcla de 0,4 g de esteroide 3 y 0,5 g de NaHCO_3 en 12 ml de cloruro de metileno se trato con 0,34 g de ácido m-Cl-perbenzoico. Después de agitar durante varias horas a temperatura ambiente la reacción se diluyo con agua, y se trato con solución de tiosulfato de sodio para destruir el peroxido residual. El material orgánico se extrajo en acetato de etilo y finalmente se purifico mediante cromatografía, para suministrar 110 mg del β -epoxido 4 deseado; R_f 0,50 (tolueno-acetona 9/1) RMN (CDCl_3) δ 0,98 (t, 3, CH_3) 0,92 (t, 3, CH_3) 3,65 + 3,70 (2xm, epoxido CH's).

Compuesto 5

Una solución de 80 mg de esteroide 4 en 3 ml de THF se reflujo con 10 mg de LiAlH_4 . Después de 2 h el material de partida había desaparecido. La mezcla se apagó mediante la adición de 30 μl de una solución de Na_2SO_4 sat. Y 0,20 g de Na_2SO_4 , agitado durante 15 minutos y filtrado sobre Celita. El filtrado se concentró y el residuo se paso sobre una columna de sílice corta, para

dar 55 mg de 5; R_f 0,24 (tolueno-acetona 9/1); RMN(CDCL₃) δ 4,04 (M, 1, CHOH), 3,78 (s, 3, OCH₃) 2,85 (m, 2, CH₂ a C6), 0,92 (s, 3, CH₃).

Compuesto 6

A una solución de metanotiolato de sodio (preparada de 0,7 ml de etanotiol y 0,27 g de una dispersión de NaH al 60%) en 9 ml de DMF se agregaron 120 mg del esteroide 5. La mezcla se reflujoó durante 3 h. Luego la reacción se vertió en agua y se extrajo con etil acetato. La cromatografía del material orgánico suministró 80 mg de 6, Mp 224-226; R_f 0,30 (tolueno-acetona 8/2); RMN (CDCL₃) δ 4,00 (m, 1, CHOH), 7,12 (AR H1), 6,20 (ar H2), 6,54 (ar H4).

Compuesto 7

A una solución de 2,7 g del esteroide 3 en 20 ml de cloruro de metileno y 3 ml de piridina, se agregaron a 0°C 1,9 ml de cloruro de trimetilsililo. Después de agitar durante 1 /2 h la reacción se vertió en agua y se extrajo con acetato de etilo, para suministrar 3, 3 g de derivado sililoxi esencialmente puro 7, R_f 0,8 (heptano-

acetona 8/2); RMN (CDCL₃) δ 0,03 (s, 9, TMS), 5,68, 5,91 (2X s, CH olefina).

Compuesto 8

Una solución de 3,2 g de 7 en 25 ml de THF seco se trató a 0°C con una solución de 2,2 ml de complejo de borano-dimetilsulfuro en 20 ml de THF. La reacción fue Subsecuentemente agitada durante 2 hr a 45°C. El reactivo de exceso se destruyó mediante adición cuidadosa de 4,5 ml de etanol abs. Seguido mediante 11 ml de NaOH de 2N y 7,7 ml de peroxido de hidrogeno al 30%. La reacción se agitó durante toda la noche, se diluyo con agua y se extrajo con acetato de etilo. El producto crudo así obtenido se purificó mediante cromatografía de columna y produjo 1,7 g del α -alcohol deseado R_f 0,36 (heptano-acetona 8/2); RMN (CDCL₃) δ 4,42 (m,

1, CHOH), 0, 12 (s, 9, TMS), 0,79 (s, 3, CH₃).

Compuesto 9

Una solución de 1,6 g de 8 y 1,3 g de trifenilfosfina en 60 ml de tolueno se trató con 0,84 g de ácido p-nitrobenzoico y 0,8 ml de dietilazodicarboxilato a 0°C. Después de agitar durante 1 h la reacción se completó. La mezcla se vertió sobre solución de NaHCO₃ acuosa sat. Y se extrajo con acetato de etilo. La purificación cromatográfica dio 2,9 g de β-nitrobenzoato, R_f 0,64 (heptano-acetona 8/2); RMN(CDCl₃) δ 5,34 (m, 1, CHOC(O) Ar), 0,91 (s, 3, CH₃), 0,95 (t, 3, CH₃), 3,80 (s, 3, OCH₃). Este material se disolvió en una mezcla de 40 ml de THF-metanol (1/1 v/v) y se trató con 4 ml de una solución de NaOH 2N. Después de agitación durante 15 minutos la reacción se vertió en agua y el producto extraído se extrajo de acetato de etilo. Después de pasar a través de una columna de sílice corta se obtuvieron 1,3 g de β-alcohol 9; R_f 0,64 (heptano-acetona 8/2); RMN (CDCl₃) δ 4,31 (m, 1, CHOH).

Compuesto 10.

Una solución de 1,3 g de 9 en 30 ml de acetona se trato con 2 ml de HCL 2n. Después de 1 hora la mezcla se neutralizó mediante la adición de NaCHO₃ saturado y se concentró. El residuo se diluyó con agua y se extrajo con acetato de etilo, para suministrar 1,0 g de 10, R_f 0,10 (heptano-acetona 8/2); RMN (CDCL₃) δ 0,90 (t, 3, CH₃) 0,95 (s, 3, CH₃), 4,48 (m, 1, CHOH).

Compuesto 11

A una reducción de metanotiolato de sodio (preparada de 0,7 ml de etanotiol y 0,3 g de una dispersión de NaH al 60%) en 9 ml de DMF se agregaron 120 mg del esteroide 10. La mezcla se reflujo durante 3 h. Luego la reacción se vertió en agua y se extrajo con acetato de etilo. La cromatografía del material orgánico suministró 80 mg de 11, Mp 143-145° C (etanol-agua); R_f 0,41 (tolueno-acetona 7/13); RMN (CDCL₃) δ 4,45 (m 1, CHOH), 0,93 (s, 3, CH₃) 0,90 (t, 3, CH₃), 6,62 + 7,10 (AB, 2, H1, 2), 6,53 (D, 1, H4).

Compuesto 13.

A una solución de 29 ml de bromuro de alilmagnesio 1 M en éter se agregaron 80 m de THF seco. A -50°C se agregaron 10 g de 7 α -propil, 16 α -alisrona -3-O-benzileter 12 en 40 ml de THF. Después de agitar durante ½ h la mezcla se le permitió entrar a temperatura ambiente y verterla en 300 ml de NH₄CL acuoso sat. El producto se extrajo con acetato de etilo y se purificó, mediante cromatografía sobre silica gel para remover los esteroisómeros suministrando 7,2 g del derivado 16 α , 17 α -dialilo 13 deseado. R_f 0,26 (heptano-etilacetato 9/1); 17 β -alil isomero R_f 0,45. RMN (CDCl₃) δ 0,88 (t, 3, CH₃) 0,96 (s, 3, CH₃), 6,08 (m, 1, CH alilo), 5,80 (m, 1, CH alilo), 4,95-5,20 (m, 4, 2x CH₂ alilo) 5,02 (CH₂OBz).

Compuesto 14

Una porción de 40 mg de dicloruro de benzilidenotris(ciclohexil)fosfinorutenio (catalizador de metátesis de Grubbs) se agregó a una solución de 450 mg de 13 en 10 ml de cloruro de metileno. Después de agitar durante 1 se agregaron 400 mg adicionales de catalizador. Después de 2 h, el solvente se removió se

reemplazó mediante 20 ml de tolueno y la mezcla se agitó con 5 g de alumina básica a 60°C para absorber el catalizador. Después de la filtración sobre Celita lavado con tolueno y etil acetato, se obtuvieron 400 mg de 14 casi puro; R_f 0,34 (heptano-etil acetato 8/2); R_f 13 0,45, en RMN ($CDCl_3$) δ 5,02 (s, 2, CH_2O), 5,97 (s, 2 $CH=CH$), 0,97 (s, 3, CH_3).

Compuesto 15

A una solución de 340 mg de 14 en 0,5 ml de cloruro de metileno se agregaron 8 μ l de piridina, 0,14 ml de H_2O_2 acuoso al 30% seguido mediante 2 mg de metiltrioxorenio. Después de agitar durante 1 h la epoxidación se completó, conduciendo predominantemente al β -epoxido deseado así como también algún α -isomero. La mezcla se vertió en agua y $Na_2S_2O_3$ saturado se extrajo con etil acetato. La cromatografía suministró 230 mg de 15 80 mg de α -epoxido indeseado. R_f 0,36 (tolueno-etilacetato 95/5; para referencia: R_f Compuesto 14: 0,39). RMN ($CDCl_3$) δ 3,31, 3,38 (m, 2, $CH(O)CH$).

Compuesto 16

Una mezcla de 4,2 g de 15 y 350 mg de LiAlH_4 en 20 ml de THF seco se reflujo durante 2 h. Luego la mezcla se enfrió subsecuentemente se trato con 1 ml de Na_2SO_4 acuoso sat; 28 ml de acetal de etilo y 8 g de Na_2SO_4 . Después de agitar durante ½ h a temperatura ambiente la reacción se filtró sobre celita el filtrado se concentró y se cromatografio, para suministrar 3,4 g de 16, Mp 147-148°C, R_f 0,20 (tolueno-etilacetato 8/2); R_f 23 0,55). RMN (CDCl_3) δ 4,25 (s, amplio, 1, CHOH), 0,90 (s, 3, CH_3), 0,86 (t, 3, CH_3), 5,02 (s, 2, OCH_2Ar).

Compuesto 17; (= 7 α , 16 β , 17 α , 22S)-7-propil-16,24-ciclo-19,21-dinacola-1,3,5(10)-trieno-3,17,22-triol.

Una solución de 3,3 g de 16 en 200 ml de etanol se hidrogeno en la presencia de 300 mg de Pd/C al 5%. Después de completar la reacción el catalizador se filtró sobre celita, y se concentró el solvente. El residuo se trituro con éter, y luego con agua, para proporcionar 1,7 g de 17; Mp 146-147°C, R_f 0,53 (tolueno-etilacetato 1/1; R_f 16 0,60). RMN (CDCl_3) δ 4,26 (s amplio, 1, CHOH) 7,14, 6,62 AB, 2, H1, H2) 6,54 (d, H4).

Ensayos para actividad estrogénica in Vitro.

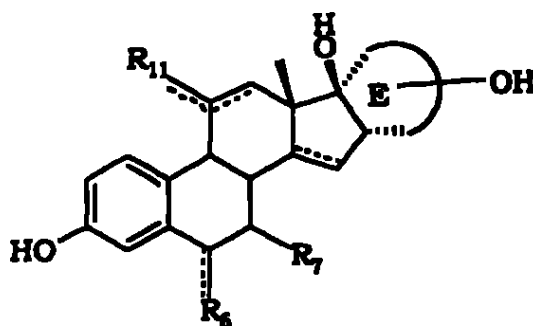
Los compuestos son ensayados para su actividad de receptor de estrógeno en un ensayo de unión en un ensayo de trans activación utilizando un receptor α o β de estrógeno humano.

La unión competitiva al receptor de estrógeno human citoplasmático α β de células de ovario de hámster Chino recombinantes (CHO) para estimar la afinidad de unión relativa (=RBA) (proporción de potencia) de un compuesto de ensayo comparado con (17 β)-estradiol (E_2) para los receptores α o β de estrógenos presentes en el citosol de las células CHO recombinantes, establemente transfectadas con el receptor α de estrógeno humano (hER α) o el receptor β (hER β).

La actividad estrogenica y anti estrogenica de los compuestos se determina en bioensayos in vitro con células de ovario de hámster chino recombinantes (CHO) establemente co-transfectadas con receptor α o β de estrógeno humano (hER α) (hER β), el promotor de oxitocina de rata (RO) y el gen reportero luciferaza (LUC). La

transactivación agonista esrogénica (proporción de potencia) del compuesto de ensayo para estimular la transactivación de la enzima luciferaza mediada por vía de los receptores de estrógeno hER α o hER β se compara con el estradiol de estrógeno estándar. La actividad antiestrogénica (proporción de potencia) del compuesto de ensayo para inhibir la transactivación de la enzima luciferaza⁵ mediada por vía de los receptores estrógeno hER α o hER β mediante el (17 β)-estradiol se compara con el ICI estándar 164.384 (= (7 α , 17 β)-N-butil-3,17-dihidroxi-N-metilestra-1,3,5(10)-trieno-7-undecanamida.

Resultados:



Fórmula 3

Compuest o como forma 3	R ₇	R ₁₁	Anillo 6 (n=1) o anillo 5 (n=0)	Ensayo de unión Er α /Er β	Transactiv ación Er α /Er β	Selectivi dad agonista Er α /Er β
A	H	H	Anillo 6	8,6/0,3	5,5/0,2	27
B	CH ₃	H	Anillo 6	20/5,2	16/< 0,1	> 160
C(=11)	C ₂ H ₅	H	Anillo 5	18/14	12/< 0,1	> 120
D	C ₂ H ₅	H	Anillo 6	17/8,7	11,5/< 0,1	> 115
E(=17 ¹¹)	C ₃ H ₇	H	Anillo 6	42/13,9	26/<0,1	> 260
F	H	C ₃ H ₇	Anillo 5	16,3/0,4	11/0,2	55

1) 17 es Org 41621

El compuesto 17 tiene en los ensayos antagonistas una proporción de selectividad Er α /Er β de símbolo < 0,1/67

Un compuesto de la técnica anterior de acuerdo con la Fórmula 3, pero sin 22-hidroxi que tiene R₇ α -propilo, R₁₁ hidrogeno y un anillo E de 6 miembros, que se denomina (7 α , 16 β , 17 α)-7-propil-16,24-ciclo-19,21-dinorcola-1,3,5 (10)-trieno-3,17-diol, tiene una proporción Er α /Er β en los ensayos de unión de 15/7 y en el ensayo de transactivación agonista 0,3-<0,1.

Ensayo para la prevención de perdida de hueso inducida por ovariectomia en ratas (ensayo anti-osteoporosis).

Introducción.

La ovariectomía de ratas induce pérdida de hueso, lo cual es debido a la deficiencia de estrógeno. La administración de compuestos estrogénicos evita este efecto. El ensayo se utiliza para evaluar un compuesto para actividad anti-osteoporósica en ratas ovariectomizadas (OVX). El efecto sobre la masa del hueso se puede evaluar mediante tomografía computarizada cuantitativa periférica (pQCT), mediante análisis cuantitativo de fotos de rayos X. Plasma osteocalcina y deoxipiridinolina urinaria, calcio y fosfato dan información sobre metabolismo del hueso. Incrementar el peso uterino y disminuir el cuerpo del peso de timo refleja el efecto estrogénico.

Animal de ensayo

Ratas Wistar hembras vírgenes maturas de 225-250 g.
Sapa:Hd/Cpd: Wu, raza SPF por Harlan, CPB, Zeist, Holanda

Experimento

En el día 1 del experimento las ratas se pesan y se distribuyen sobre jaulas en orden de peso corporal, mediante el cual la rata con el peso corporal más pequeño se ubica en la primer jaula la rata mas pesada en la jaula final. Los tratamientos son aleatorios sobre las ratas.

La operación Sham y la ovariectomia se desarrollan bajo anestesia con éter. Después de la recuperación de la anestesia, dentro de, las 24 h, el vehículo, el compuesto de referencia o el compuesto de ensayo se administran una vez dos veces diariamente durante 4 semanas. Durante este periodo las ratas son pesadas semanalmente. Después en 4 semanas se desarrolla la autopsia. En la autopsia las ratas son anestesiadas con éter en la sangre y se recolectan de la aorta abdominal. Ambos femorales, los vertebrados L1L2L3L4 (opcionalmente), el útero, el timo, el hígado, los riñones, las glándulas adrenales, tiroides, y pituitaria son disectadas. La dimensión de la densidad mineral del hueso y la geometría del fémur derecho se desarrollan mediante pQCT en el día de la autopsia sobre tejido fresco. La densidad mineral del hueso trabecular de la parte metafiseal el fémur (FBMDDIS

mg/cm³) se mide con un pQCT(máquina de tomografía computarizada cuantitativa periférica; XCT 960A, Stratec, Birkenfeld, Alemania).

Interpretación de los resultados

La Ovariectomia origina una disminución estadísticamente significativa en la densidad del hueso distal el volumen del hueso trabecular del fémur e incrementa de manera estadísticamente significativa en el plasma los niveles de Osteocalcina y deoxipiridinolina urinaria ($P \leq 0,05$, 2 veces ANOVA).

Los compuestos de ensayo son considerados por ser activos cuando los valores de densidad de hueso medio del fémur distal son significativamente incrementados comparados con el grupo de control ovariectomizado. Los efectos de los compuestos sobre los niveles de desoxipiridinolina urinaria reflejan un efecto sobre la resorción del hueso, efectos sobre los niveles de osteocalcina del plasma reflejan un efecto sobre el cambio del hueso y pueden ayudar a entender el mecanismo de acción.

La dosis activa mínima (MAD) es la dosis donde la diferencia proporcional media en la densidad mineral del hueso trabecular entre 40 y 60% se alcanza.

Referencias.

Wronski T. J. y Yen C. F.: de ovariectomised rat as an animal model for postmenopausal bone loss. Cells and Material, Supp. 1 (1991): 69-76. Yamazaki I. and Yamaguchi H.: Characteristics of an ovariectomised osteopenic rat model. J. Bone Min. Res. 4 (1989): 12-22. Ederveen A. G. H. and Kloosterboer H. J.: Tibolone, a steroid with a tissue-specific hormonal profile, completely prevents ovariectomy-induced bone loss in sexually mature rats. J. Bone & Mineral Research Vol 14, pp 1963-1970, 1999.

Resultados:

Compuesto 17 (Org 41621): Ensayo de osteoporosis oral 30 μ /kg.

Compuesto de la técnica anterior (7^α, 16β, 17^α)-7-propil-16, 24-ciclo-19,21-dinorcola-1,3,5(10)-trieno-3,17-diol:190 µg /kg por oral.

Ensayo para actividad estrogénica in vivo

La actividad estrogénica in vivo se determinó por medio del ensayo de Allen Doisy, descrito en F. Allen, L. A. Doisy, J. AMER. Med. Assoc., 81,819-821(1923)

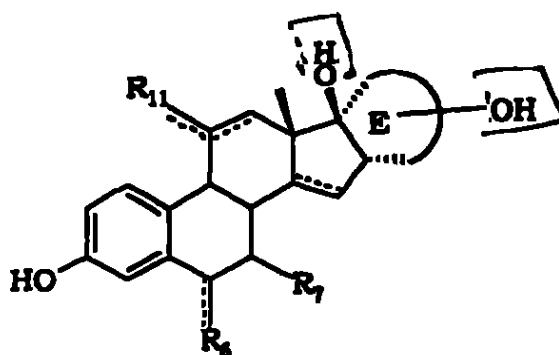
Resultados:

Compuestos 17 (Org 41621): Allen Doisy sc 5 µg/kg, oral 30 µg/kg.

Compuesto técnica anterior (7^α, 16β, 17^α)-7-propil-16,24-ciclo-19,21-dinorcola-1,3,5(10)-trieno-3-17-diol:
Allen Doisy sc 24 µg/kg, oral 125 µg/kg.

REIVINDICACIONES

1. Compuesto esteroide que tienen la Fórmula (1):



Fórmula 1

Donde:

Los enlaces punteados representan dobles enlaces opcionales;

R_6 es H, $=CH_2$, o $-CH_3$, o CH_2-CH_3 ,

R_7 es H, alquilo C_{1-4} , alquenilo C_{2-5} alquinilo C_{2-5} en donde los grupos alquilo, alquenilo o alquinilo pueden ser sustituidos con 1 a 3 átomos de halogeno independientemente escogidos del grupo de átomos de fluor o cloro;

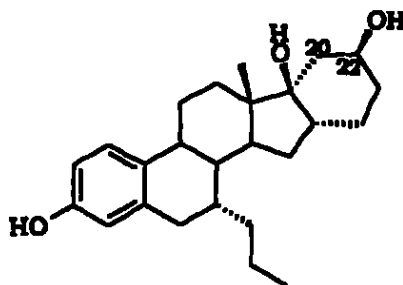
R₁₁ es H, alquilo C₁₋₄, alqueno C₂₋₄, alquino C₂₋₄ o alquilideno C₁₋₄, en donde el grupo alquilo, alqueno, alquino o alquilideno se pueden sustituir con 1 a 3 átomos de halógeno independientemente escogidos del grupo de átomos de fluor cloro;

E representa junto con los átomos de carbono 16 y 17 del esqueleto de esteroides un anillo de 4 a 7 miembros, dicho anillo tiene una configuración α en cis con respecto al esqueleto esteroide, opcionalmente comprende 1 o 2 enlaces endocíclicos;

O una prodroga de este.

2. Compuesto esteroide de acuerdo con la reivindicación 1, caracterizado por que R₆ es H, R₇ es alquilo C₁₋₃, el anillo E es un anillo de 6 miembros sin dobles enlaces que tengan un hidroxil en la posición 22 en la estereoconfiguración S.

3. El compuesto esteroide de acuerdo con la reivindicación 1 o 2, caracterizado por que el compuesto esta de acuerdo a la Fórmula 2



Fórmula 2,

Denominado (7 α , 16 β , 17 α), 22S)-7-propil-16,24-ciclo-19,21-dinorcola-1,3,5(10)-triano-3,17,22-triol,

4. Un compuesto esteroide de acuerdo con cualquiera de las reivindicaciones 1-3 para uso en terapia.

5. Un método para modificación selectiva de la actividad de receptores de estrógeno al poner en contacto un compuesto de acuerdo cualquiera de las reivindicaciones 1-3 con receptores de estrógeno.

6. El método de acuerdo a la reivindicación 5, caracterizado por que el método es un método no médico.

7. El método de acuerdo a la reivindicación 5 o 6, caracterizado por que el método es una modificación

selectiva de la actividad de los receptores α de estrógeno al poner en contacto un compuesto de acuerdo con cualquiera de las reivindicaciones 1-3 con los receptores α de estrógeno.

8.  El método de acuerdo a la reivindicación 5 o 6, caracterizado por que el método es una modificación selectiva de la actividad de receptores β de estrógeno al poner en contacto un compuesto de acuerdo a cualquiera de las reivindicaciones 1-3 con los receptores β de estrógeno.

9.  Uso de un compuesto esteroide de acuerdo a cualquiera de las reivindicaciones 1-3 para la elaboración de un medicamento para un tratamiento relacionado con receptor de estrógeno selectivo.

10.  El uso de acuerdo a la reivindicación 9, caracterizado por que el tratamiento relacionado con el receptor de estrógeno selectivo es la prevención o tratamiento de quejas peri-menopausicas o post-menopausicas.

11. El uso de acuerdo a la reivindicación 9, caracterizado por que el tratamiento relacionado con receptor de estrógeno es un tratamiento contraceptivo.

12. Composición farmacéutica que comprende el compuesto esteroide de acuerdo a cualquiera de las reivindicaciones 1-3 y un auxiliar farmacéuticamente aceptable.

RESUMEN

La invención describe un compuesto que tiene la Fórmula (1), en donde los enlaces en línea punteada representan enlaces dobles opcionales; R_6 es H, $=CH_2$, o $-CH_3$, o CH_2-CH_3 ,

R_7 es H, alquilo C_{1-4} , alquenilo C_{2-5} alquinilo C_{2-5} en donde los grupos alquilo, alquenilo o alquinilo pueden ser sustituidos con 1 a 3 átomos de halógeno independientemente escogidos del grupo de átomos de fluor o cloro;

R_{11} es H, alquilo C_{1-4} , alquenilo C_{2-4} , alquinilo C_{2-4} o alquilideno C_{1-4} , en donde el grupo alquilo, alquenilo, alquinilo o alquilideno se pueden sustituir con 1 a 3

átomos de halógeno independientemente escogidos del grupo de átomos de fluor cloro;

E representa junto con los átomos de carbono 16 y 17 del esqueleto de esteroides un anillo de 4 a 7 miembros, dicho anillo tiene una configuración α en cis con respecto al esqueleto esteroide, opcionalmente comprende 1 o 2 enlaces endocíclicos; o una prodroga del mismo. Tales compuestos pueden ser usados en terapias, o para métodos de modificación selectiva de la actividad de receptores de estrógeno.



FORMATO DE DIGITALIZACION
RELACION DE ANEXOS

Ronyl
Technologies S.A.
Integración de Soluciones Digitales

92

Expediente No		No de Folio
Item	No de unidades	
1	CD	✓
2	DVD	
3	REVISTA	
4	LIBRO	
5	PERIODICO	
6	DISQUETES	
7	SOBRE DE MANILA	
8	SOBRE BLANCO TAMAÑO CARTA	3
9	SOBRE BLANCO TAMAÑO OFICIO	
10	OTROS:	
Observaciones: Dete T-may		

97-AS
5

CAVELIER
ABOGADOS
 EDIFICIO SISKI
 CARRERA 4ª N° 72-35
 BOGOTÁ, 8- COLOMBIA

CESION

Yo, (nosotros), abajo firmado(s)

L **ZEN, Hubert, Jan, Jozef**

domiciliado (s) en _____

Meerhoek 602
5403 AC UDEN
The Netherlands

declaro(amos) bajo juramento ser único(s) y verdadero(s)
 inventor(es) de la invención:

**"16, 17-CARBOCYCLIC CONDENSED STEROID COMPOUNDS HAVING SELECTIVE ESTROGENIC
 ACTIVITY"**

**COMPUESTOS ESTEROIDES CONDENSADOS 16,17-CARBOCICLICOS QUE TIENEN ACTIVIDAD
 ESTROGENICA SELECTIVA**

declaro(amos) así mismo que cedo(amos) y transfiero
 (erimos), sin limitación, a favor de la sociedad _____

Akzo Nobel N.V.

constituida y existente de conformidad con las leyes de

The Netherlands

domiciliada en _____

Velperweg 76

6824 BM ARNHEM

The Netherlands

todos los derechos inherentes a dicha invención y
 que los citada Compañía queda facultada para
 solicitar en su nombre la patente correspondiente
 en la República de Colombia.

Dado y firmado hoy/Given and signed this

L **ZEN, Hubert, Jan, Jozef**

en/in

h/ nov / 2002

Firma

ASSIGNMENT

I (we), the undersigned

LOOZEN, Hubert, Jan, Jozef

of _____

Meerhoek 602
5403 AC UDEN

HOLANDA

state(s) under oath to be sole and true inventor(s) of the
 invention:

state as well, that assign, without reservations or
 limitations in favour of _____

Akzo Nobel N.V.

a corporation constituted and existing in conformity
 with the laws of _____

HOLANDA

domiciled in _____

Velperweg 76

6824 BM ARNHEM

HOLANDA

all rights inherent to said invention and that the above
 mentioned company hereby is enabled to apply, in its
 name, for the corresponding patent in the
 Republic of Colombia

Signature

gu

(Legalization required)

(Legalización necesaria)

AUTENTICACION NOTARIAL (INDIVIDUE)

NOTARIAL AUTHENTICATION (INDIVIDUAL)

A los días del mes de _____ de 20____
ante mí, Notario Público de _____
compareció(eron) personalmente _____

On this_ day of _____ 20____
before me, a Notary Public of _____
personally appeared _____

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

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

Notario Público Notary Public

NOTA: LA AUTHENTICACION CONSULAR ES NECESARIA.

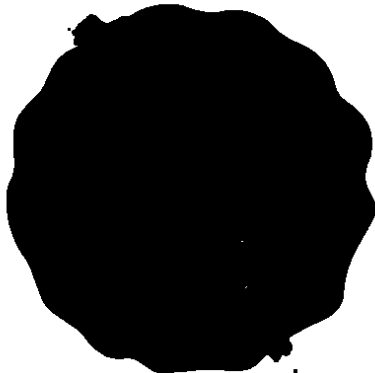
Seen by me, mr. Robbert Alexander Gallas, civil-law notary practising in The Hague,
for the authentication of the signature on the attached document of:

- Mr Hubert Jan Jozef Loozen, born on the twenty-fourth of August
nineteenhundred fourty-eight in Heerlen, The Netherlands, residing at Uden, The
Netherlands, holder of a Dutch passport, number N88066956

The Hague, the nineteenthth day of November twothousandtwo.



A long, flowing handwritten signature in black ink, extending from the notary seal to the right.



All instructions are carried out on the basis of an agreement as meant in Section 400 of Book 7
of the Dutch Civil Code by Pels Rijcken & Droogleevers Fortuijn, a partnership consisting of
private companies with limited liability. The agreement is subject to terms of business registered
with the District Court at The Hague. A limitation of liability is included in these terms of
business. The terms of business will be provided on request. These can also be accessed at
www.prd.nl.

A P O S T I L L E

(Convention de La Haye du 5 octobre 1961)

1. Pais: NEDERLAND
El presente documento público
2. ha sido firmado por mr. R.A. Gallas
3. quien actúa en calidad de notario en
's-Gravenhage
4. y está revestido del sello/timbre de el susodicho
notario

Certificado

5. en 's-GRAVENHAGE 6. el día 21 november 2002
7. por de Griffier van de Arrondissementsrechtbank
8. bajo el número: 2002-3344
9. Sello/timbre: 10. Firma:



m mdeerp

[Handwritten signature]

TRADUCCIÓN OFICIAL No. 05.12/02c realizada por Diego Vargas, Traductor Oficial, Resolución No. 0001 de 1999 del Ministerio de Justicia y registrado ante el Ministerio de Relaciones Exteriores de Colombia.

Documento de Cesión escrito en inglés y español por medio del cual LOSEN, Hubert, Jan, Jozef domiciliado en Meerhoek 602, 5403 AC UDEN, Holanda, declara bajo juramento ser único y verdadero inventor de la invención:

COMPUESTOS ESTEROIDES CONDENSADOS 16,17-CARBOCÍCLICOS QUE TIENEN ESTROGÉNICA SELECTIVA

y declara así mismo que cede y transfiere, sin limitación, a favor de la sociedad Akzo Nobel N.V. constituida y existente de conformidad con las leyes de HOLANDA domiciliada en Velperweg 76, 6824 BM ARNHEM, Holanda todos los derechos inherentes a dicha invención y que dicha Compañía queda facultada para solicitar a su nombre la patente correspondiente en la República de Colombia.

Dado y firmado hoy

LOSEN, Hubert, Jan, Jozef

en Firma Ilegible 12/Nov/2002

(Anexo)

El Señor Robbert Alexander Gallas, Notario Público ejerciendo en La Haya, vio el anterior documento para la autenticación de la firma en el adjunto de:

El Señor Hubert Jan Jozef, nacido el veinticuatro de agosto de mil novecientos cuarenta y ocho en Heerlen, Holanda, residente

Diego F. Vargas
DIEGO F. VARGAS Z.

TRADUCTOR E INTERPRETE OFICIAL
ESPAÑOL - INGLES -- INGLES - ESPAÑOL
RES. 0001 DE ENERO 4 DE 1999
MINISTERIO DE JUSTICIA

97
en Uden, . Holanda, portador del Pasaporte Holandés, número
N88066956

La Haya, el diecinueve de noviembre de dos mil dos.

Sello Notarial: Sr. R.A. GALLAS NOTARIS TE 's-GRAVENHAGE

Firma Ilegible

Sello de oblea ilegible

Todas las instrucciones se realizan basadas en un acuerdo, según se establece en la Sección 400 del Libro 7 del Código Civil Holandés por Pels Rijcken & Droogleever Fortuijn, una sociedad conformada por sociedades privadas de responsabilidad limitada. El acuerdo está sujeto a los términos de actividades registradas ante el Tribunal del Distrito en La Haya. Se incluye una limitación de responsabilidad en estos términos de actividades. Los términos de actividades serán suministrados a petición. Estos también pueden ser consultados en www.prd.nl.

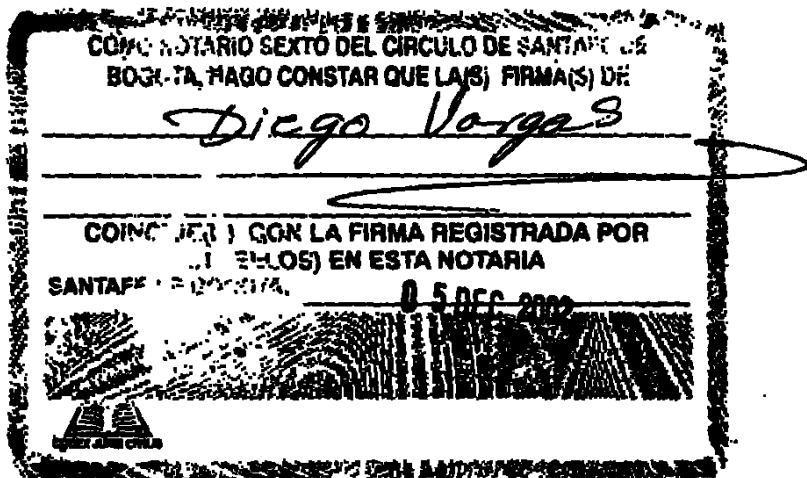
(RESPALDO)

Apostille en español de Holanda certificada el 21 de noviembre de 2002 en 's-GRAVENHAGE por Griffier van de Arrondissementsrechtbank con el número: 2002-3344.

Es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.

DVZ/ID: 3958/WPCL002G/COLO 11214-841-003-1

Diego F. Vargas
DIEGO F. VARGAS Z.
TRADUCTOR E INTERPRETE OFICIAL
ESPAÑOL - INGLES - INGLES - ESPAÑOL
RES. 0001 DE ENERO 4 DE 1999
MINISTERIO DE JUSTICIA



NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2002 DEC - 12 12:52

JEFE DE OFICINA
SANTAFE DE BOGOTA

MINISTERIO DE RELACIONES
EXTERIORES

Diego F. Arango

032371

CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPENA
LAS FUNCIONES DE



Industria y Comercio

SUPERINTENDENCIA

Radicación : 02110304 00000000
 Fecha (AMB): 2002-12-05 17:06:29
 Trámite : 011 PCT-PATENT 379 FASE NUCT 411 PRESENTAC
 Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

HIT : 800176089-2

RECIBO OFICIAL DE CAJA : 02 - 75,603
 FECHA : NOVIEMBRE 13 DE 2002

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	3136955	13/11/2002	15,849,560.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	378,000.00
	TOTAL :	\$ 378,000.00

SOM: TRESCIENTOS SETENTA Y OCHO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Colo 11214-841-003-1

Carrera 13 No. 27-00 Pisos 5, 7 y 10
 Conmutador 382 0840
 Fax 350 5220
 E-mail: info@sic.gov.co
 www.sic.gov.co
 Bogotá, D.C., Colombia

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION	()	()
MODELO DE UTILIDAD	()	()
Indicación de que se solicita la concesión de una patente.	()	()
Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	()
Descripción de la invención.	()	()
Dibujos de ser estos pertinentes.	()	()
Comprobante de Pago de las tasas establecidas.	()	()

COMPLETA () INCOMPLETA ()

DISEÑO INDUSTRIAL ()

- Indicación de que se solicita el registro de Diseño Industrial	()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.	()	()
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	()	()
Comprobante de pago de las tasas establecidas	()	()

COMPLETA () INCOMPLETA ()

ESQUEMA DE TRAZADO ()

- Indicación de que 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 de trazado	()	()
Comprobante de pago de las tasas establecidas.	()	()

COMPLETA () INCOMPLETA ()

Firma Responsable:

Fecha: Radicación : 02118504 00000000 Folios: 96
Fecha (AMD): 2002-12-05 17:06:29
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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Folios 100-102
Extracts pub here.
llz-June/04



2020
Bogotá, D.C.,

Doctor:
Emilio Ferrero
Apoderado
AKZO NOBEL N.V.

Oficio N° 06848

ASUNTO:	Radicación N°	02-110504
	Solicitud Internacional	PCT/EP01/04868
	Fecha inicio fase nacional	08/01/2003
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

☐ La solicitud no contiene la traducción de los anexos del reporte de examen preliminar internacional (Art. 38.2.b) del tratado PCT).

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA BESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha 22 ABO. 2003.