

FORMULARIO UNICO DE CORRECCIONES Y MODIFICACIONES
2000-10

1

SOLICITUD DE:

☐ Corrección de Error Material

☒ Modificación a una Solicitud

2
SOLICITANTE

Nombre: SCHERING KTIENGESELLSCHAFT

Dirección: Müllerstrasse 178
13353 Berlin, Alemania

Teléfono: _____ Fax: _____

E-Mail: _____

Domicilio: BERLIN, ALEMANIA

IDENTIFICACIÓN

C.C. ☐ NIT ☐

C.E. ☐ Otro ☐

Número _____

3
**REPRESENTANTE
O APODERADO**

Nombre: GUSTAVO HOLLMANN RESTREPO

Dirección: Cra. 11ª No.94-78. Oficina 308
Bogotá, D.C., Colombia.

Teléfono: 6161948 Fax: 6163976

E-Mail: _____

IDENTIFICACIÓN

C.C. ☒ NIT ☐

C.E. ☐ Otro ☒

Número 2878023 TP 5903

4 **Numero de Expediente:** 00 065517

5 **Descripción de la corrección o modificación solicitada:** Que se inscriba el traspaso que ha hecho la sociedad JENAPHARM GMBH & CO. KG, domiciliada en Jena, Alemania, a la sociedad SCHERING AKTIENGESELLSCHAFT, domiciliada en Berlin, Alemania, de la solicitud de patente referente a:
"MESOPROGESTINAS (MODULARES DE RECEPTORES DE PROGESTERONA) COMO
COMPONENTES DE ANTICONCEPTIVOS FEMENINOS", Expediente No. 00 065517.

6 **Comprobante de pago No.** 33,184 **Fecha:** Mayo 13 de 2003

7 **Anexos:**

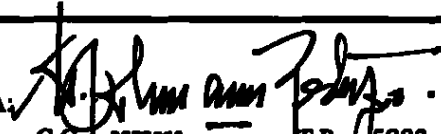
☒ Comprobante de pago de la tasa

☒ El poder con que obro. Se encuentra protocolizado en ese despacho bajo el No. 605.

☒ Los documentos de cesión respectivos.

8

NOMBRE: GUSTAVO HOLLMANN RESTREPO

FIRMA: 
C.C. 2878023 T.P. 5903

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

11115

134 148

SUB-ADMINISTRACION Y COMERCIO
Radicación : 0006551/ 00000005 Folios: 14
Fecha (MM): 2003-05-13
Trámite : 002 PRIENTES D 1 REGISTRO/ 329 COMPLETOS
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 33,184
FECHA : MAYO 13 DE 2003

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
GUSTAVO HOLLMAN	CONSIGNACION	BANCO POPULAR	050-00110-6	11724172	13/05/2003	5,098,000.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50003-01-03 CAMBIO DE MODALIDAD Y MODIFICA	
	12 MARCAS Y LEÑAS COMERCIALES	82,000.00
	TOTAL :	82,000.00

SON: OCHENTA Y DOS MIL PESOS

RESPONSABLE : _____

Modificación de patente.
Expediente n° 00 065517

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

135 129

COLOMBIA

Documento de transferencia de patentes
Document of Assignment of Patents

La abajo firmante
the undersigned

JENAPHARM GMBH & CO KG

residente en
residing at

**Otto-Schott-Strasse 15
07745 Jena - Alemania**

propietaria de las solicitudes de patente indicadas en el listado adjunto
owner of the patent applications mentioned on the attached listing

declara por el presente, que cede, vende y transfiere en toda propiedad y dominio a
declare hereby that they cede, sell and transfer all rights of ownership to

SCHERING AKTIENGESELLSCHAFT

domiciliada en Müllerstrasse 178 - 13353 Berlin - Alemania
residing at

las referidas solicitudes de patente por la suma de
of the above patent applications in consideration of

así como todos los derechos y prerrogativas que a ellas se refieren y corresponden sin
as well as all rights and privileges relating or corresponding thereto without
excepción de ninguna clase, pudiendo por consiguiente de hoy en adelante la cesionaria
exception of any kind so that for the future the above mentioned assignee
ambas nombrada, considerarse única dueña de ellas como mejor conviniere a sus
may consider himself the only owner with rights to trade or dispose as
intereses, sin que haya lugar a reclamo ulterior alguno al respecto por parte de
it may suit his interests and no ulterior claim on the part of

JENAPHARM GMBH & CO KG

en ningún caso y en ningún

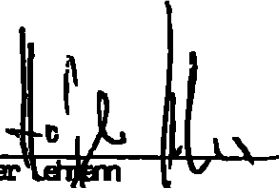
will be considered for any cause or at any time By the present document

tiempo Por el presente acto el adquirente acepta la transferencia y faculta asimismo a
the assignee accepts this assignment and appoints

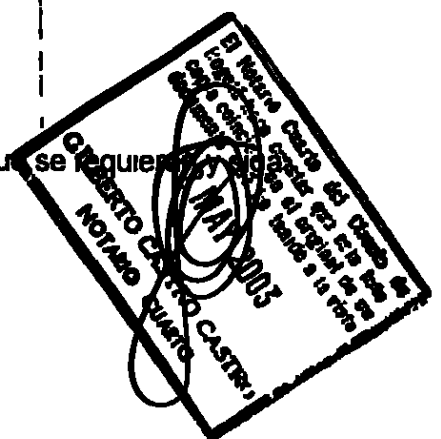
para que haga inscribir esta transferencia, pida los testimonios que se requieren
to have the transfer recorded to file the necessary testimonials and prosecute
hasta su terminación los trámites de este asunto
this matter until its complete termination.

Dado y firmado en


Dr. Dieter Taubert
Managing Director


Holger Lehmann
Head of Finance and Accounting

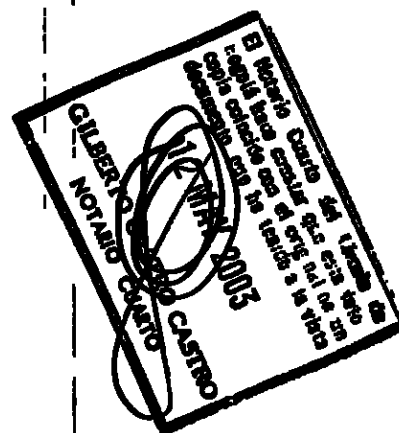
Jenapharm GmbH & Co KG



136 150

Listado adjunto a documento de transferencia

<u>Fecha de presentación</u>	<u>Acta No</u>	<u>Título</u>
31 08 2000	00065517	Mesoprogestinas (Moduladores de Receptores de Progesterona) como componentes de anticonceptivos femeninos
31 08 2000	00065516	Mesoprogestinas (moduladores de receptor de progesterona) como componentes de composiciones utilizadas para la Terapia de Sustitución Hormonal (TRH)
31 08 2000	00065515	Mesoprogestinas (moduladores de receptores de progesterona) para el tratamiento y la prevención de trastornos ginecológicos benignos hormona-dependientes



137 151

UR-Nr 125 / 2003

State of Thüringen)
SS
City of Jena)

On the 17th day of February, 2003 personally
appeared before me at Jenapharm GmbH &
Co KG in 07745 JENA, Otto-Schott-Str 15

1 Herr Dr. Dieter Ulrich Alfred TAUBERT
geb am 10.01.1952
wohnhaft in Weimar und

both personally known to me undersigned

I as Notary Public certify that above named persons per-
sonally acknowledged before me that they executed
their signature on the reverse page of this document.

In accordance with Sec 21 of the Federal Regulation
relating to the practice of Notaries Public, I hereby
hereby certify, that -

based on the certified copy (Issued by the County
Court of GERA / Thüringen) dated July 25
2002 of the commercial register - File No HR B 1386)
for Jenapharm GmbH & Co. KG and

based on the certified copy (Issued by the County Court
of ERFURT / Thüringen) dated July 25 2002
of the commercial register for Schering Verwaltungs-
gesellschaft mbH (File No HR B 8994)
Dr Dieter TAUBERT - as its executive manager
(" Geschäftsführer ") has the right of its sole represen-
tation and that the company is authorized to represent
Jenapharm GmbH & Co. KG as its personally liable
partner and that Mr Holger LEHMANN signed the
aforementioned document in his capacity as authorized
signatory (Prokurist) and as Head of Finance and
Accounting

IN WITNESS WHEREOF, I have hereunto set
my hand and affixed my official seal the day and
year of this certificate first above written

Jena, February 17, 2003

Freistaat Thüringen)
SS
Stadt Jena)

Am 17 Februar des Jahres 2003 erschienen vor
mir in den Geschäftsräumen der Jenapharm
GmbH & Co KG in 07745 Jena, Otto-Schott-Str 15

2 Holger LEHMANN
geb am 21.12.1949
geschäftsmässig Otto Schott Str 15 JENA

beide dem Notar von Person bekannt

Als öffentlicher Notar bestätige ich hiermit, daß vorbe-
zeichnete Personen anerkannt, das umseitige Doku-
ment persönlich unterschrieben zu haben

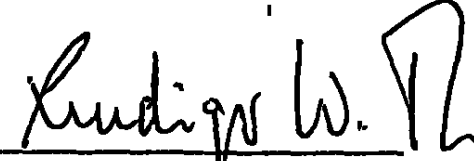
Gemäß § 21 Bundesnotarordnung bescheinige ich,
der Notar, aufgrund der von mir heute eingesehenen
Handelsregisterauszüge, nämlich

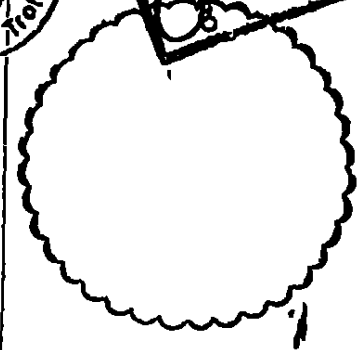
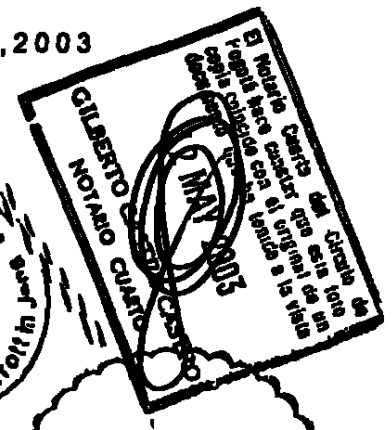
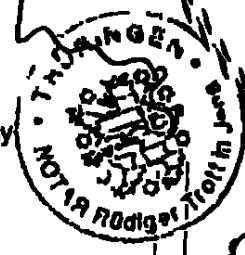
des vom Registergericht GERA beglaubigten Handelsre-
gisterauszuges vom 04.07.2002 zu HR A 1386
(für die Jenapharm GmbH & Co. KG) und

sowie aufgrund des vom Registergericht ERFURT be-
glaubigten Handelsregisterauszuges vom 25.07.2002
zu HR B 8994 (für die Schering Verwaltungsgesell-
schaft mbH) die Alleinvertretungsbefugnis der Herren
Dr Dieter TAUBERT als Geschäftsführer der Schering
Verwaltungsgesellschaft mbH, die wiederum als per-
sönlich haftende Gesellschafterin die Jenapharm
GmbH & Co. KG vertritt und daß Herr Holger LEHMANN
das bezeichnete Dokument unterschrieb in seiner
Eigenschaft als Prokurist und als Head of Finance
and Accounting

Zum Zeichen dafür habe ich dies Dokument
unterschrieben und mit meinem Amtssiegel
versehen am vor bezeichneten Datum

Jena, den 17 Februar, 2003


Rüdiger W. TROTT
Notary Public - Notar
Leutragraben 2-4, 07743 JENA / Germany



138

Apostille

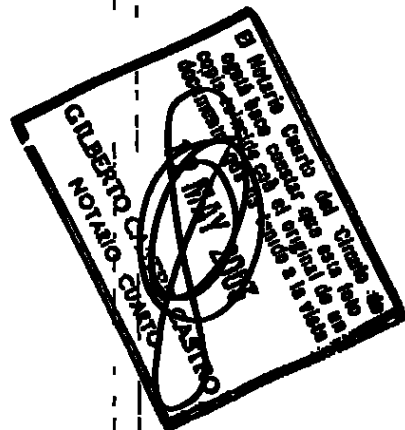
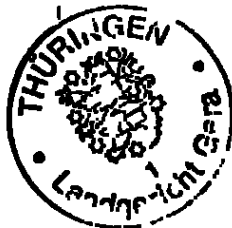
(Convention de La Haye du 5 octobre 1961)

- 1 Land Bundesrepublik Deutschland
Diese öffentliche Urkunde
- 2 ist unterschrieben von Herrn Trott
- 3 in seiner Eigenschaft als Notar
- 4 sie ist versehen mit dem Siegel des
Herrn Notar Rüdiger Trott

Bestätigt

- 5 In Gera
- 6 am 24 02 2003
- 7 durch Vizepräsidenten des Landgerichts
- 8 unter Nr 910 E1 - 40/2003
- 9 Siegel
- 10 Unterschrift

Reinhard Maul
Reinhard Maul



139 152

Traducción Oficial del Alemán de la certificación, la nota de gastos y la apostilla adjuntas al Documento de Transferencia de Patentes suscrito entre la compañía *Jenapharm GmbH & Co KG* domiciliada en Jena, Alemania y la compañía *Schering Aktiengesellschaft* domiciliada en Berlín, Alemania

Registro Notarial Número 125/2003

Estado de Thüringen, Ciudad de Jena

El día 17 de Febrero del 2003 ante el suscrito Notario comparecieron personalmente en las Oficinas de *Jenapharm GmbH & Co KG* en 07745 Jena, Otto-Schott-Str 15

- 1 Sr Dr Dieter Erich Alfred TAUBERT,
nacido el 10 01 1952, domiciliado en Weimar, y
- 2 Holger LEHMANN, nacido el 21 12 1949,
con domicilio comercial en Otto Schott Str 15, Jena

ambos conocidos personalmente por el suscrito notario

En mi calidad de Notario certifico que las personas arriba mencionadas reconocieron haber firmado el documento adjunto

De conformidad con el Artículo 21 de La Disposición Notarial Federal y luego de revisar la fotocopia autenticada del Registro Comercial HRA 1386 del Juzgado Municipal de Jena fechada el 04 07 2002 (a nombre de *Jenapharm GmbH & Co KG*) y luego de revisar la fotocopia autenticada del Registro Comercial 8894 del Juzgado Municipal de Erfurt fechada el 25 07 2002 (a nombre de *Schering Verwaltungsgesellschaft*),

certifico que el Señor Dr Dieter TAUBERT está autorizado para representar individualmente a la compañía *Schering Verwaltungsgesellschaft mbH*, la cual a su vez representa como socia personalmente garante a la compañía *Jenapharm GmbH & Co KG*, y



140
153

que el Señor Holger LEHMANN firmó el documento adjunto en su
calidad de Apoderado y Jefe de Finanzas y Contabilidad

En testimonio de lo cual coloco aquí abajo mi firma y mi sello
oficial en la fecha arriba escrita

Jena, Febrero 17 del 2003

Rüdiger W Trott, Notario Público
Leutgraben 2-4, 07743 Jena/Alemania
(Firma y Sello Oficial)

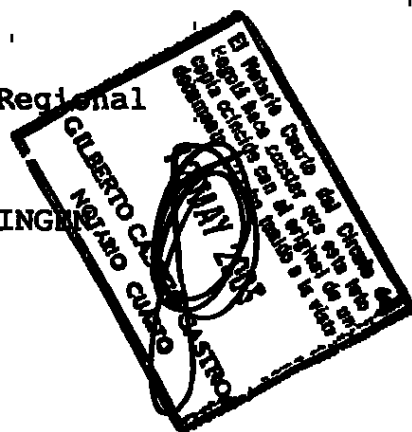
APOSTILLA

(Convención de La Haya del 5 de Octubre de 1961)

- 1 País República Federal de Alemania
Este documento público
- 2 Ha sido firmado por El Señor Trott
- 3 En su calidad de Notario
- 4 Y lleva el sello Del Señor Notario Rüdiger Trott

Confirmado

- 5 En Gera
- 6 El día 24 02 2003
- 7 Por El Vicepresidente del Tribunal Regional
- 8 Bajo el No 910 E1 - 40/2003
- 9 Sello Tribunal Regional Gera - THÜRINGEN
- 10 Firma Reinhard Maul




ADOLF WATZKE
Traductor Oficial
Res 8432 Minjusticia

10115716/15

141 154

HCO

COLOMBIA

Documento de transferencia de patentes
Document of Assignment of Patents

La abajo firmante
the undersigned

JENAPHARM GMBH & CO KG

residente en
residing at

Otto-Schott-Strasse 15
07745 Jena - Alemania

propietaria de las solicitudes de patente indicadas en el listado adjunto
owner of the patent applications mentioned on the attached listing

declara por el presente, que cede, vende y transfiere en toda propiedad y dominio a
declare hereby that they cede sell and transfer all rights of ownership to

SCHERING AKTIENGESELLSCHAFT

domiciliada en Müllerstrasse 178 - 13353 Berlin - Alemania
residing at

las referidas solicitudes de patente por la suma de
of the above patent applications in consideration of
así como todos los derechos y prerrogativas que a ellas se refieren y corresponden sin
as well as all rights and privileges relating or corresponding thereto without
excepción de ninguna clase, pudiendo por consiguiente de hoy en adelante la cesionaria
exception of any kind so that for the future the above mentioned assignee
ambas nombrada, considerarse única dueña de ellas como mejor conviniere a sus
may consider himself the only owner with rights to trade or dispose as
intereses, sin que haya lugar a reclamo ulterior alguno al respecto por parte de
it may suit his interests and no ulterior claim on the part of

JENAPHARM GMBH & CO KG

en ningún caso y en ningún
will be considered for any cause or at any time By the present document
tiempo Por el presente acto el adquirente acepta la transferencia y faculta asimismo a
the assignee accepts this assignment and appoints

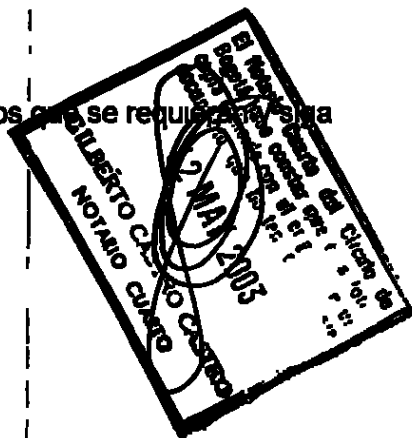
para que haga inscribir esta transferencia, pida los testimonios que se requieran y siga
to have the transfer recorded to file the necessary testimonials and prosecute
hasta su terminación los trámites de este asunto
this matter until its complete termination.

Dado y firmado en

Schering Aktiengesellschaft

Dr. Schwarz
ppa
Confidential Clerk

Dr. Klose
ppa
Confidential Clerk



El Notario Público en el momento de
hacer esta copia ha verificado que
esta coincide con el original de su
documento. 12 MAY 2003
GILBERTO CASTRO
NOTARIO CUARTO

MINISTERIO DEL INTERIOR

440637
7 de 7/10/03

NO SE ASUME
RESPONSABILIDAD

2003 MAY -8 A 3:39

1208

143 156ⁿ

Urkundenrolle-Nr R 40/2003

Ich habe das Mitwirkungsverbot nach § 3 Abs 1 Nr 7 BeurkG erläutert Meine Frage, ob eine Vorbefassung im Sinne der Vorschrift vorliege, wurde verneint

Die vor mir geleisteten Unterschriften

des Herrn Dr Norbert S c h w a r z,
geboren am 8 November 1943,

und des Herrn Dr Walter K l o s e,
geboren am 26 Dezember 1952,

beide geschäftsansässig in 13353 Berlin, Mullerstraße 178,

- von Person bekannt -

beglaubige ich

Zugleich bescheinige ich auf Grund heutiger Einsicht in die Akten des Handelsregisters beim Amtsgerichts Charlottenburg zur Geschäftsnummer HR B 283, daß die vorgenannten Herren Dr Schwarz und Dr Klose als Prokuristen gemeinsam zur Vertretung der Schering Aktiengesellschaft, Berlin, berechtigt sind.

Berlin, 21 Januar 2003

Notar

Kostenberechnung gem. §§ 141, 154 KostO

Geschäftswert 12.000,00 €

Beglaubigungsgebühr §§ 32, 45 I

Wegegebühr gem § 58

Gebühr für die Vertreterbescheinigung gem § 150

Schreibauflagen §§ 136, 152

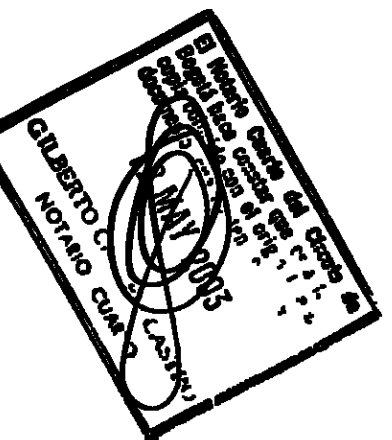
Postauslagen §§ 137, 152

16 % Mehrwertsteuer

Berlin, 21 Januar 2003

Notar

15,00 €
15,00 €
13,00 €
1,50 €
1,44 €
45,94 €
7,35 €
53,29 €



144 157

101 a E - F

Apostille
(Convention de La Haye du 5 octobre 1961)

1 Land Bundesrepublik Deutschland

Diese öffentliche Urkunde

2 ist unterschrieben von Dimitri R e m p e n

3 in seiner Eigenschaft als Notar

4 sie ist versehen mit dem Siegel
des Notars

Bestätigt

in Berlin

6 am 28 Januar 2003

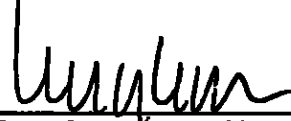
7 durch den Präsidenten des Landgerichts in Berlin

8 unter Nr 9101 a E - F 149/2003

9 Siegel

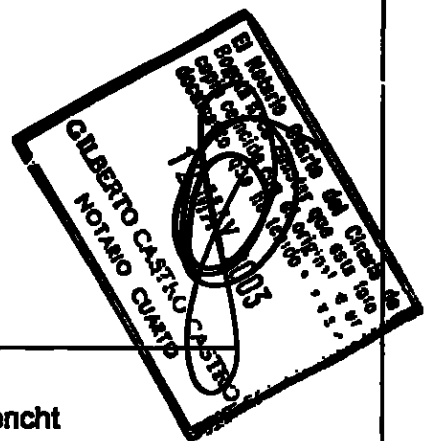
10 Unterschrift

Im Auftrage



(Kupfernagel)

Vorsitzender Richter am Landgericht



145 150

Traducción Oficial del Alemán de la certificación, la nota de gastos y la apostilla adjuntas al Documento de Transferencia de Patentes suscrito entre la compañía *Jenapharm GmbH & Co. KG* domiciliada en Jena, Alemania y la compañía *Schering Aktiengesellschaft* domiciliada en Berlín, Alemania.

Registro Notarial Número R 40/2003

Habiendo explicado la prohibición de participación conforme al Artículo 3 inciso 1 Numeral 1 de la Ley de Notarización, yo les pregunté a las participantes si existe algún impedimento en el sentido de dicha Ley. La respuesta fue negativa.

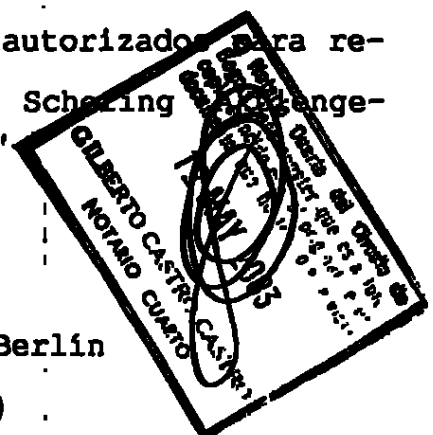
Autentico las firmas que aparecen anteriormente, las cuales fueron ejecutadas en mi presencia y pertenecen al

Señor Dr. Robert Schwarz, nacido el 8 de Noviembre de 1943, y al Señor Dr. Walter Klose, nacido el 26 de Diciembre de 1952 ambos conocidos personalmente por el suscrito notario y domiciliados comercialmente en 13353 Berlín, Müllerstraße 178.

Al mismo tiempo, luego de la revisión hecha hoy en el Registro Comercial HRB 283 del Juzgado Municipal de Charlottenburg, certifico que los mencionados Señores Dr. Schwarz y Dr. Klose en su calidad de Apoderados se encuentran autorizados para representar conjuntamente a la compañía *Schering Aktiengesellschaft* domiciliada en Berlín.

Berlín, 21 de Enero del 2003

Dimitri Rempen, Notario en Berlín
(Firma y Sello Oficial)



----- (continúa en la 2ª página) -----

146 159

Nota de gastos según Artículos 141,154 Disposición Impuestos:

Valor del negocio: 12.000,00 EUROS

Impuesto Artículo 32, 45I Disp. Impuestos	15,00 EUROS
Impuesto Artículo 58 Disp. Impuestos	15,00 EUROS
Impuesto Artículo 150 Disp. Impuestos	13,00 EUROS
Impuesto Artículos 136, 152 Disp. Impuestos	1,00 EUROS
Impuesto Artículos 137, 152 Disp. Impuestos	1,44 EUROS
I.V.A. 16%	7,35 EUROS
Total:	53,29 EUROS

Berlín, 21 de Enero del 2003

Dimitri Rempen, Notario (firma)

APOSTILLA

(Convención de La Haya del 5 de Octubre de 1961)

1. País: República Federal de Alemania
Este documento público
2. Ha sido firmado por: Dimitri Rempen
3. En su calidad de: Notario
4. Y lleva el sello: Del mencionado Notario

Confirmado

5. En: Berlín
6. El día: 28 de Enero del 2003
7. Por: El Presidente del Tribunal Regional
8. Bajo el No.: 9101 a E-F 149/2003
9. Sello: EL PRESIDENTE DEL TRIBUNAL REGIONAL EN BERLIN
10. Firma: Por encargo: Kupfernagel,
Juez Presidente en el Tribunal Regional



Adolf Watzke
ADOLF WATZKE
Traductor Oficial
 Res. 2433 Minjusticia

MINISTERIO DE INTERIORES

440631
Asio G w h k e
LAS FUENTES

NO SE ASIME
MINISTERIO DE INTERIORES

2003 MAY -2 14 3 52
cells
LAS FUENTES

El Estado Cuero del Cinto de
ago-3 de 1963 con el original de
documento que se tiene a la vista
12 1410005
GILBERTO CASTRO CASTRO
GUAYMO CUARTO

147 160

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

2020

Bogotá, D.C., 20 de octubre de 2005

Apoderado: Gustavo Hollmann Resterpo

Oficio: 001 9934

ASUNTO	Radicación: 00-65517
	Trámite 002
	Evento 001
	Actuación 430
	Folios

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

Documentos estudiados:

- ♦capítulo descriptivo, folios 2 a 31;
- ♦capítulo reivindicatorio, folios 32 a 36;
- ♦1º examen de forma, folio 59;
- ♦respuesta técnica al 1º examen de forma, folios 61 y 62 ;
- ♦solicitudes de las cuales se reivindica prioridad, folios 63 a 116;
- ♦2º examen de forma, folio 142;
- ♦solicitud del examen de patentabilidad 145 y 146.

Objeto de la Invención:

El título de la invención es "MESOPROGESTINAS (MODULADORES DE RECEPTORES DE PROGESTERONA) COMO COMPOENTES DE ANTICONCEPTIVOS FEMENINOS".

El objeto de la presente solicitud se refiere a un método terapéutico de anticoncepción usando mesoprogestinas y/o moduladores de receptores de pregeserona.

Reivindicaciones de uso

De acuerdo con la legislación colombiana el uso que se reclama en las reivindicaciones 1 a 21 (folios 32 a 34) no se considera para protección por patente, como se lee en el artículo 14 de la Decisión 486 de la Comisión de la

Comunidad Andina"... Los Países Miembros otorgarán patentes para las invenciones sean de **productos o procedimientos** en todos los campos de la tecnología..."; AQUÍ NO se hace alusión al uso.

Continuando con la última parte del Artículo 14"... (Los Países Miembros otorgarán patentes para las invenciones sean de **productos o procedimientos** en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial." El hecho que se diga que el producto o el procedimiento tengan aplicación industrial no quiere decir que la aplicación industrial sea susceptible de patente.

Así mismo, citando **completamente** el artículo 19 este reza: " Se considerará que una **Invención (léase producto o procedimiento)** es susceptible de aplicación industrial (*una característica de la invención*) cuando su objeto puede ser producido o utilizado en cualquier clase de industria, entendiéndose por industria la referida a cualquier actividad productiva, incluidos los servicios." Esta diciendo que una invención, producto o procedimiento, debe servir para algo. En ningún momento se dice que un uso pueda ser protegido como patente.

El artículo 16 dice: " Los productos o procedimientos (*o sea, los inventos, nótese que nunca se refieren a nada diferente*) ya patentados comprendidos en el estado de la técnica de conformidad con el Artículo 21 de la presente Decisión, no serán objeto de nueva patente por el simple hecho de atribuirse un uso distinto al originalmente comprendido por la patente inicial." Nunca se refieren a una protección para el uso, como erróneamente se podría interpretar. Se trata de no conceder nueva patente a un invento (exclusivamente productos o procedimientos) al que se le ha encontrado nueva función, pero que se trata exactamente del mismo producto o procedimiento. Es decir, si el compuesto, aparato, etc. o método ya esta dentro del estado de la técnica, el hecho que se haya descubierto una nueva aplicación para el mismo compuesto, aparato, etc. o método, implica que no es merecedor de nueva patente, o que el nuevo uso le reestablezca la novedad. En ningún caso se dice que se esta protegiendo el uso. Simplemente se dice que el producto o procedimiento ya esta dentro del estado de la técnica y una utilización diferente no esta contemplada para permitir conceder patente al producto o al procedimiento nuevamente.

Los usos o segundos usos no son patentables, de conformidad con la sentencia del TJAC 89-AI-2000, los usos en general no son patentables.

-La reivindicación 22, 29 no es clara, ni esta delimitada, porque los términos "mesoprogesterin" y "estrogeno", son términos genericos, que encierran muchas

estructuras químicas y todas no están enteramente soportadas en la descripción.

-Las reivindicaciones 25, 26, 27, 28 no son ~~de~~ claras, puesto que una composición no se puede caracterizar por el suministro de placebos u otras sustancias o el uso por periodos de tiempo, eso es característico de un método de tratamiento.

-Las reivindicaciones 30, 31, no es clara, porque se encabeza como una composición, como unidad integral no puede estar en forma de dos o más unidades separadas son dos o mas composiciones independientes.

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la Decisión 486 de la Comunidad Andina establece que: ***"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"***.

En cumplimiento del artículo 14 de la Decisión 486, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio. reivindicaciones 22 a 38, folios 34 a 38. Consultada la fuente de información con que cuenta este despacho se encontró los siguientes documentos:

Item	Documento	Fecha de publicación	Título
D1	US5693628	02-dic-1997	11-Benzaldoxime-estra-diene derivatives, methods for their production and pharmaceuticals containing these compounds.
D2	DE 4332284	23-mar-1995	Neue 11-benzaldoxim-17 β -methoxy-17 α -methoxymethyl-estradien-derivate, verfahren zu ihrer herstellung und diese verbindungen enthaltende Arzneimittel
D3	WO 9612494	02-may-1996	Competitive progesterone antagonists for regulating female fertility as required
D4	WO9741866	13- nov-1997	Improvement of implantation rates after in vitro fertilization
D5	WO9749407	31-dic-1997	Progestogen-anti-progestogen regimens.
D6	WO9805679	12-feb-1998	Mixed antagonists of the progesterone receptor and assays therefor

Evaluación de la novedad:

El artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina dispone que: *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica".*

En la solicitud en estudio reclama composiciones y metodos terapeuticos donde se usan mesopregestinas y un estrogeno

-La anterioridad D1 a D6 describen composiciones que comprenden mesoprogestinas individuales y estrogenos, y también composiciones específicas que comprenden ambos componentes en una sola composición, además el uso común de los estrogenos y mesoprogestinas es para la anticoncepción femenina. (Observar particualrmente las partes que estan remarcadas en cada una de las anterioridades adjuntas.)

Tal como puede verse las compsiciones reclamadas en la solictud en estudio no son nueva, como es nuevo que su uso como anticonceptivo femenino.

No	Documento:	Reivindicaciones afectadas:	Requisito afectado:
D1	US5693628	22 a 38	Novedad
D2	DE4332284	22 a 38	Novedad
D3	WO9612494	22 a 38	Novedad
D4	WO9741866	22 a 38	Novedad
D5	WO9749407	22 a 38	Novedad
D6	WO9805679	22 a 38	

En cumplmiento del artículo 45 de la decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

151 164

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 No. 10 de 2001.


ALIX CARMENZA CÉSPEDES/DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha
13 OCT. 2015

CONCEPTO TÉCNICO No. 1674	EXAMINADOR TÉCNICO Código No. 202012
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D1

152 165



US005693628A

United States Patent [19]

Schubert et al.

[11] Patent Number: 5,693,628

[45] Date of Patent: Dec. 2, 1997

[54] 11-BENZALDOXIME-ESTRA-DIENE
DERIVATIVES, METHODS FOR THEIR
PRODUCTION AND PHARMACEUTICALS
CONTAINING THESE COMPOUNDS

[75] Inventors: Gerd Schubert; Günther Kaufmann;
Lothar Sobock; Michael Ostel, all of
Jena; Walter Elger, Berlin; Anstoll
Karlshagen, Jena, all of Germany

[73] Assignee: Jenapharm GmbH, Jena, Germany

[21] Appl. No.: 389,175

[22] Filed: Sep. 20, 1994

[51] Int. Cl.⁶ A61K 31/56; C07J 1/00

[52] U.S. Cl. 514/179; 552/648

[58] Field of Search 514/177, 179,
514/178; 552/611, 642, 648

[56] References Cited

U.S. PATENT DOCUMENTS

4,829,060	5/1989	Ottow et al.	514/179
4,871,724	10/1989	Green et al.	514/173
4,912,097	3/1990	Thutach et al.	514/172
5,089,635	2/1992	Noef et al.	549/297
5,272,140	12/1993	Locant	514/172
5,276,023	1/1994	Mogulowsky et al.	514/179
5,407,928	4/1995	Kersch et al.	514/179
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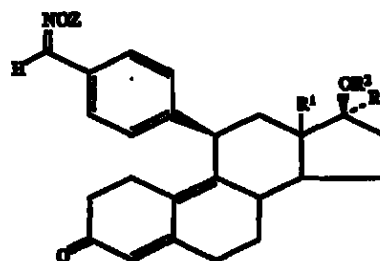
FOREIGN PATENT DOCUMENTS

1310630 11/1992 Canada.
2130515 3/1995 Canada.
2130516 3/1995 Canada.

Primary Examiner—Shean C. Wu
Attorney, Agent, or Firm—Flicaler, Dubb, Meyer & Lovejoy
LLP

[57] ABSTRACT

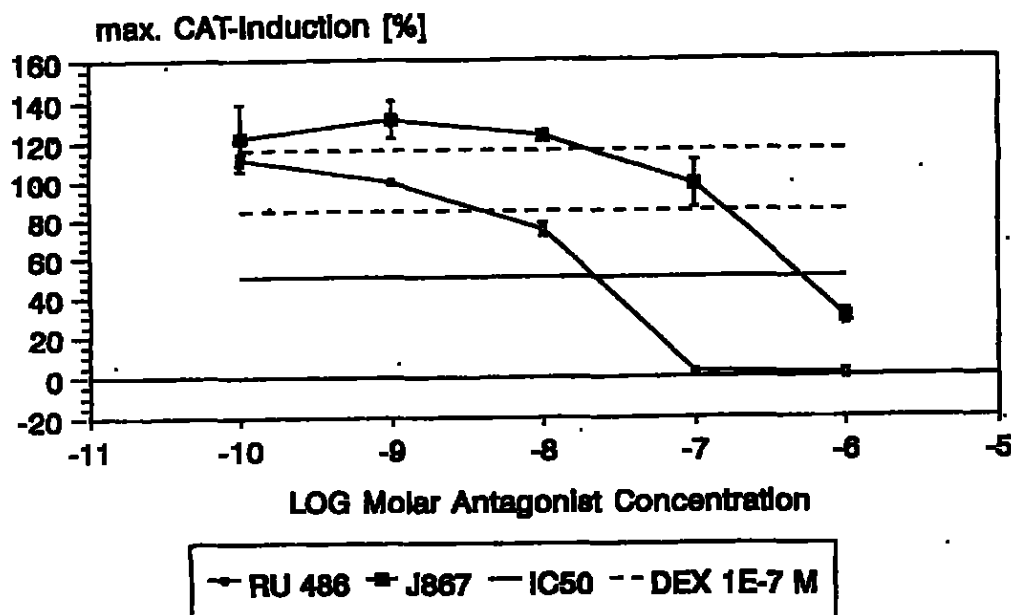
This invention relates to new 11-benzaldoxime-estra-diene
derivatives of the general formula I



and their pharmaceutically acceptable salts, a method for
their production, and pharmaceuticals containing such com-
pounds.

The compounds described show strong antigonadotropic
effects combined with reduced glucocorticoid activity.

15 Claims, 3 Drawing Sheets



Antigonadotropic effect of J 867 compared with RU 486.
Inhibition of CAT induction in the 2R75/AR-763 line of
human mammary cells induced by 10⁻⁷ M dexamethasone.

11-BENZALDOXIME-ESTRA-DIENE DERIVATIVES, METHODS FOR THEIR PRODUCTION AND PHARMACEUTICALS CONTAINING THESE COMPOUNDS

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to new 11-benzaldoxime-estradiene derivatives, methods for their production, and pharmaceuticals containing these compounds.

2. Description of the Prior Art

11 β -substituted phenyl estradienes are known. Patent specification EP 057 115 describes the production of 11 β -aryl-17 α -propyl estradiene-4,9-dienes, and patent specification DE 3 504 421 describes the reaction of 11 β -(4-formyl phenyl)-estra-4,9-diene-3-ones with hydroxylamines. Both the 11 β -formyl phenylene residue and the 3-keto group are oxidized according to the cited method. In addition, syn and anti isomers are formed at C-3. Nothing is known as yet about the effects of the described compounds.

Progesterone is secreted during menstruation, and in large amounts by the ovary and the placenta during pregnancy. Its regulatory significance has perhaps not been clarified in every respect.

What is safely known is that progesterone, together with oestrogens, produces the cyclic changes in the uterine mucosa during the menstrual cycle and pregnancy. After ovulation, an increased level of progesterone causes the uterine mucosa to adopt a condition that permits the embedding of an embryo (blastocyst). Conservation of the tissues in which the embryo grows is also dependent on progesterone.

A dramatic change in the muscular function of the uterus takes place during pregnancy. Response of the gravid uterine muscle to hormonal and mechanical stimuli that induce labour in the non-gravid state is strongly reduced or non-existent. There can be no doubt that progesterone has a key function here, despite the fact that at certain stages of pregnancy, e.g. shortly before giving birth, there is a high reactivity even at high blood-progesterone concentrations.

Very high progesterone levels are also reflected by other typical processes during pregnancy. The composition of the mammary glands and the obstruction of the cervix until shortly before the date of birth-giving may serve as examples of this.

Progesterone contributes subtly to controlling ovulation processes. It is known that high doses of progesterone have anti-ovulatory qualities. They result from an inhibition of the hypophyseal gonadotropin secretion which is a prerequisite for the maturation of the follicle and for its ovulation. But on the other hand, it can be seen that the comparatively small quantity of progesterone secreted by the maturing follicle plays an active part in preparing and triggering ovulation. Hypophyseal mechanisms (temporary, so-called positive feedback of progesterone to gonadotropin secretion) appear to have a great significance in this respect (Loutch, D.; Human Reproduction 6, 1991, 1238-1240).

The doubtlessly existing functions of progesterone in the maturing follicle and luteal corpus themselves have been less well analyzed. It can be assumed, eventually, that there are both stimulating and inhibiting effects on endocrine functions of the follicle and the luteal corpus.

It may also be assumed that progesterone and progesterone receptors are of great importance for pathophysiological processes. Progesterone receptors have been found in

endometriotic focuses, but also in tumours of the uterus, the mamma, and the CNS (meningiomas). The role of these receptors in conjunction with the growth behaviour of these pathologically relevant tissues is not necessarily dependent on progesterone levels in the blood. It has been proved that substances characterized as progesterone antagonists such as RU 486-Mifepristone (EP-0 057 115) and ZK 98299-Onapristone (DE-OS-35 04 421) tend to trigger far-reaching functional changes even at negligible levels of progesterone in the blood. It appears to be possible that modifications of the transcriptional effects of the progesterone receptor that is not filled with progesterone are decisive in this respect (Chwalisz, K. et al., Endocrinology, 129, 317-322, 1991).

The effects of progesterone in tissues of the genitals and in other tissue are brought about by interaction with the progesterone receptor. In a cell, progesterone bonds to its receptor with high affinity. This causes changes in the receptor protein: conformational changes, dimerization of 2 receptor units to form one complex, binding of the receptor's DNA bonding place by dissociating a protein (HSP 90), bonding to hormon-responsive DNA elements. Eventually, the transcription of certain genes is regulated. (Gronemeyer, H. et al., J. Steroid Biochem. Molec. Biol. 41, 3-8, 1992).

The effect of progesterone or progesterone antagonists does not only depend on their concentration in the blood. The concentration of receptors in a cell is strongly regulated as well. Oestrogens stimulate the synthesis of progesterone receptors in most tissues. Progesterone inhibits the synthesis of oestrogen receptors and that of its own receptor. It is assumed that this interaction of oestrogens and gestagens goes to explain why gestagens and antigestagens can influence oestrogen-dependent processes without being bonded by the oestrogen receptor. These relations are naturally of great importance for the therapeutical application of antigestagens. These substances appear to be appropriate for directly influencing female reproductive processes, e.g. for preventing nidation after ovulation, or for increasing uterine reactivity to prostaglandins and oxytocin in a later pregnancy, or for achieving metecrurys and cervix softening ("maturing").

Antigestagens inhibit ovulation in various species of subhuman primates. The mechanism of this effect has not yet been elucidated. Among the hypotheses discussed are an inhibition of gonadotropin secretion, and ovarian mechanisms based on disturbing para- and autocrine functions of progesterone in the ovary.

Antigestagens are capable of modulating or weakening the effects of oestrogens although the majority of them does not have any oestrogen receptor affinity at the cytoplasmic level, and although they can cause an increase of the oestrogen receptor concentration. Similar effects in endometriotic focuses or tumorous tissue equipped with oestrogen and progesterone receptors justify the expectation of a favourable influence on pathologic conditions. Particular advantages with regard to exerting a favourable influence on pathologic conditions such as endometriosis might be achieved if an inhibited ovulation supplemented the inhibiting effects of an antigestagen acting in the tissue. Ovarian hormonal products and their stimulating effect on the pathologically altered tissue would also be reduced by inhibiting ovulation. It would be desirable to inhibit ovulation in severe cases of endometriosis to bring the tissue in the genital tract which would normally be in constant reconstruction, into a reversible state of rest.

A method is being discussed with regard to contraception according to which an antigestagen treatment suppresses

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ovulation, and secretory transformation of the endometrium is induced by subsequent gestagen treatment. The days of treatment with antigestagens and gestagens and the treatment-free days result in a 28-day cycle with a regular withdrawal bleeding (Banika, E. E., *Advances in Contraception* 7, 345-51, 1991).

Antigestagens can have different hormonal and anti-hormonal properties. Anti-glucocorticoid properties are of particular therapeutical relevance. These are unfavourable for therapeutical applications mainly aimed at inhibiting progesterone receptors as they have undesired side effects when applied at the dosage required for such therapy which may prevent the application of a therapeutically sensible dose, or require that treatment be discontinued. Partial or complete reduction of anti-glucocorticoid properties is an important prerequisite for a therapy using antigestagens, especially with indications that require therapy over several weeks or months.

BRIEF DESCRIPTION OF THE DRAWINGS

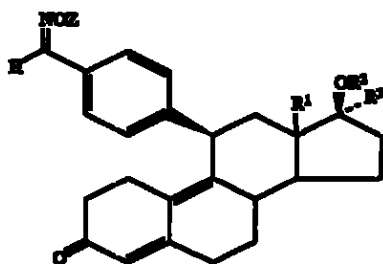
FIG. 1. is a chart showing a comparison of the influence on uterine weight in cyclic guinea pigs when treated with the antigestagen agents RU 486, a control (the vehicle), and a compound of the present invention, J 867 (as prepared in accordance with Example 1). The chart shows dosage in mg/animal/day on the x-axis versus uterine weight ratio (experimental weight versus control weight).

FIG. 2. is a graph showing the antiglucocorticoid effect of J 867 (Example 1) in comparison to RU 486. The graph depicts the inhibition of CAT induction in a human mammary cell line (the ZR75/AGP-763 cell line) which were induced by 10^{-6} M dexamethasone. The graph indicates the log molar antagonist concentration in the x-axis versus the maximum CAT induction as a percentage in the y-axis. The results for dexamethasone is shown as dashed lines (- - -), the IC50 is shown in solid line (—), RU 486 is shown as open boxes (□), and J 867 is shown with closed boxes (■).

FIG. 3. is a graph showing the antiglucocorticoid effect of J 867 (Example 1) in comparison to RU 486. The graph depicts the inhibition of TAT induction in a rat hepatoma cell line (the H4-IIE cell line) which were induced by 10^{-6} M dexamethasone. The graph indicates the log molar antagonist concentration in the x-axis versus the maximum TAT induction as a percentage in the y-axis. The results for dexamethasone is shown as dashed lines (- - -), the IC50 is shown in solid line (—), RU 486 is shown as open boxes (□), and J 867 is shown with closed boxes (■).

SUMMARY OF THE INVENTION

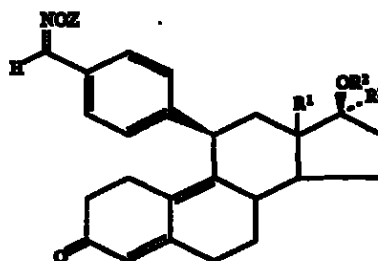
It is the purpose of this invention to provide new 11 β -benzaldehyde-estra-4,9-diene derivatives of the general formula I



and its pharmaceutically acceptable salts as well as a method for producing them. It is another purpose of this invention to

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provide pharmaceuticals containing a compound of the general formula I or its pharmaceutically acceptable salt. In general formula I,



R¹ is a hydrogen atom or alkyl residue containing 1-6 carbon atoms,

R² is a hydrogen atom, an alkyl, aryl, aralkyl, or alkylaryl group containing 1-10 carbon atoms, an acyl residue containing 1-10 carbon atoms, or a residue -CONHR⁴ or -COOR⁴,

where R⁴ is a hydrogen atom, an alkyl, aryl, aralkyl, or alkylaryl residue containing 1-10 carbon atoms,

R³ is a hydrogen atom, an alkyl, aryl, aralkyl, or alkylaryl group containing 1-10 carbon atoms,

a residue -(CH₂)_n-CH₂X, where n=0, 1, or 2, X represents a fluorine, chlorine, bromine, or iodine atom, a cyano, azido, or rhodano group, a residue OR⁵ or SR⁵,

R⁵ being a hydrogen atom, an alkyl, aryl, aralkyl, or alkylaryl residue containing 1-10 carbon atoms, or an acyl residue containing 1-10 carbon atoms,

a residue OR⁶, in which R⁶ has the meaning specified above,

a residue -(CH₂)_n-CH=CH(CH₂)_p-R⁷, where n=0, 1, 2, or 3 and p=0, 1, or 2, and R⁷ represents a hydrogen atom, an alkyl, aryl, aralkyl, or alkylaryl group containing 1-10 carbon atoms, a hydroxyl group, an alkoxy or acyloxy group containing 1-10 carbon atoms,

a residue -(CH₂)_q-C=CR⁷, where q=0, 1, or 2, and R⁷ represents a hydrogen atom, a fluorine, chlorine, bromine, or iodine atom, an alkyl, aryl, aralkyl, or alkylaryl residue containing 1-10 carbon atoms, or an acyl residue containing 1-10 carbon atoms,

Z represents a hydrogen atom, an alkyl, aryl, aralkyl, or alkylaryl residue containing 1-10 carbon atoms, or an acyl residue containing 1-10 carbon atoms, a residue -CONHR⁴ or -COOR⁴, where R⁴ is a hydrogen atom, an alkyl, aryl, aralkyl, or alkylaryl residue containing 1-10 carbon atoms, or an alkaline or alkaline-earth metal atom.

Preferred are compounds in which R¹ is a methyl or ethyl group,

R² represents a hydrogen atom, an alkyl group containing 1-10 carbon atoms, an acyl residue containing 1-10 carbon atoms, or a residue -CONHR⁴ or -COOR⁴, where R⁴ is a hydrogen atom, an alkyl or aryl residue containing 1-10 carbon atoms,

R³ is a hydrogen atom, an alkyl, aryl, aralkyl, or alkylaryl group containing 1-10 carbon atoms,

R⁵ is a residue -(CH₂)_n-CH₂X, where n=0, 1, or 2, X represents a fluorine, chlorine, bromine, or iodine atom, a cyano, azido, or rhodano group, a residue OR⁵ or SR⁵,

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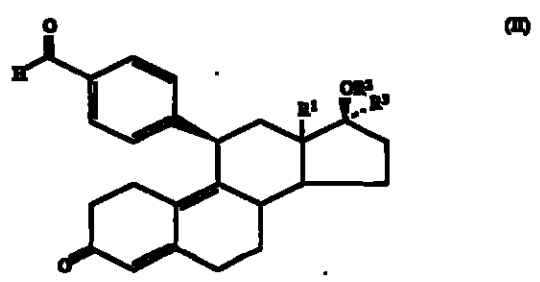
R^5 being an alkyl residue containing 1-6 carbon atoms, or an acyl residue containing 1-6 carbon atoms, a residue OR^5 ,
 R^5 being a hydrogen atom, an alkyl residue containing 1-10 carbon atoms, or an acyl residue containing 1-10 carbon atoms,
 a residue $-(CH_2)_q-CH=CH(CH_2)_p-R^6$, where $q=0, 1, 2$, or 3 and $p=0, 1$, or 2 , and R^6 represents a hydrogen atom, an alkyl group containing 1-10 carbon atoms, a hydroxyl group, an alkoxy or acyloxy group containing 1-10 carbon atoms,
 a residue $-(CH_2)_q-C\equiv CR^7$, where $q=0, 1$, or 2 , and R^7 represents a hydrogen atom, a fluorine, chlorine, bromine, or iodine atom, an alkyl residue containing 1-10 carbon atoms, or an acyl residue containing 1-10 carbon atoms, and Z represents a hydrogen atom, an alkyl residue containing 1-10 carbon atoms, an acyl residue containing 1-10 carbon atoms,
 a residue $-CONHR^4$ or $-COOR^4$, where R^4 is a hydrogen atom or an alkyl residue containing 1-10 carbon atoms, or an alkaline or alkaline-earth metal atom.
 Particularly preferred are compounds in which R^2 represents an alkyl group containing 1-6 carbon atoms, an acyl residue containing 1-6 carbon atoms, or a residue $-CONHR^4$ or $-COOR^4$, where R^4 is a hydrogen atom or an alkyl or aryl residue containing 1-6 carbon atoms,
 R^3 is a hydrogen atom or an alkyl group containing 1-6 carbon atoms,
 a residue $-(CH_2)_n-CH_2X$, where $n=0, 1$, or 2 , X represents a fluorine, chlorine, bromine, or iodine atom, a cyano, azido, or rhodano group, a residue OR^5 or SR^5 ,
 R^5 being an alkyl residue containing 1-6 carbon atoms, or an acyl residue containing 1-6 carbon atoms,
 a residue OR^5 ,
 R^5 being an alkyl residue containing 1-6 carbon atoms, or an acyl residue containing 1-6 carbon atoms,
 a residue $-(CH_2)_q-CH=CH(CH_2)_p-R^6$, where $q=0, 1, 2$, or 3 and $p=0, 1$, or 2 , and R^6 represents an alkyl group containing 1-6 carbon atoms, an alkoxy or acyloxy group containing 1-6 carbon atoms,
 or a residue $-(CH_2)_q-C\equiv CR^7$, where $q=0, 1$, or 2 , and R^7 represents an alkyl residue containing 1-6 carbon atoms, or an acyl residue containing 1-6 carbon atoms,
 and Z represents an alkyl residue containing 1-6 carbon atoms, an acyl residue containing 1-6 carbon atoms, a residue $-CONHR^4$ or $-COOR^4$, where R^4 is a hydrogen atom, an alkyl or aryl residue containing 1-6 carbon atoms.
 Most preferred are:

- 11 β -[4-(hydroximinomethyl)phenyl]-17 β -hydroxy-17 α -methoxymethyl-estra-4,9-diene-3-on,
- 11 β -[4-(hydroximinomethyl)phenyl]-17 β -hydroxy-17 α -ethoxymethyl-estra-4,9-diene-3-on,
- 11 β -[4-(hydroximinomethyl)phenyl]-17 β -hydroxy-17 α -propoxymethyl-estra-4,9-diene-3-on,
- 11 β -[4-(hydroximinomethyl)phenyl]-17 β -hydroxy-17 α -i-propoxymethyl-estra-4,9-diene-3-on,

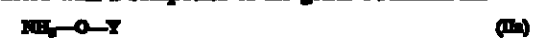
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- 11 β -[4-(hydroximinomethyl)phenyl]-17 β -methoxy-17 α -methoxymethyl-estra-4,9-diene-3-on,
- 11 β -[4-(hydroximinomethyl)phenyl]-17 β -methoxy-17 α -ethoxymethyl-estra-4,9-diene-3-on,
- 11 β -[4-(hydroximinomethyl)phenyl]-17 β -hydroxy-17 α -(3-hydroxyprop-1-yl)-estra-4,9-diene-3-on,
- 11 β -[4-(hydroximinomethyl)phenyl]-17 β -methoxy-17 α -(3-hydroxyprop-1-yl)-estra-4,9-diene-3-on,
- 11 β -[4-(hydroximinomethyl)phenyl]-17 β -hydroxy-17 α -Z-(3-hydroxypropyl)-estra-4,9-diene-3-on,
- 11 β -[4-(hydroximinomethyl)phenyl]-17 β -methoxy-17 α -Z-(3-hydroxypropyl)-estra-4,9-diene-3-on,
- 17 α -chloromethyl-11 β -[4-(hydroximinomethyl)phenyl]-17 β -hydroxy-estra-4,9-diene-3-on,
- 17 α -chloromethyl-11 β -[4-(hydroximinomethyl)phenyl]-17 β -methoxy-estra-4,9-diene-3-on,
- 17 α -cyanomethyl-11 β -[4-(hydroximinomethyl)phenyl]-17 β -hydroxy-estra-4,9-diene-3-on,
- 17 α -cyanomethyl-11 β -[4-(hydroximinomethyl)phenyl]-17 β -methoxy-estra-4,9-diene-3-on,
- 17 α -azidomethyl-11 β -[4-(hydroximinomethyl)phenyl]-17 β -methoxy-estra-4,9-diene-3-on,
- 11 β -[4-(hydroximinomethyl)phenyl]-17 β -methoxy-17 α -methoxymethyl-estra-4,9-diene-3-on,
- 11 β -[4-(methyloximinomethyl)phenyl]-17 β -methoxy-17 α -methoxymethyl-estra-4,9-diene-3-on,
- 11 β -[4-(acetoximinomethyl)phenyl]-17 β -methoxy-17 α -methoxymethyl-estra-4,9-diene-3-on,
- 11 β -[4-(methyloximinomethyl)phenyl]-17 β -hydroxy-17 α -methoxymethyl-estra-4,9-diene-3-on,
- 11 β -[4-[(ethoxycarbonyl)oximinomethyl]phenyl]-17 β -methoxy-17 α -methoxymethyl-estra-4,9-diene-3-on,
- 11 β -[4-[(ethylaminocarbonyl)oximinomethyl]phenyl]-17 β -methoxy-17 α -methoxymethyl-estra-4,9-diene-3-on,
- 17 β -methoxy-17 α -methoxymethyl-11 β -[4-[(phenylaminocarbonyl)oximinomethyl]phenyl]-estra-4,9-diene-3-on, and
- 11 β -[4-(hydroximinomethyl)phenyl]-17 β -ethoxy-17 α -ethoxymethyl-estra-4,9-diene-3-on.

This invention furthermore relates to a method for producing compounds of the general formula I and their pharmaceutically acceptable salts, characterized in that a compound of the general formula II



wherein R^1 , R^2 , and R^3 have the abovementioned meanings, is reacted with a compound of the general formula IIa



where Y is a hydrogen atom, an alkyl residue containing 1-10 carbon atoms, an acyl residue containing 1-10 carbon atoms, or a residue $-CONHR^4$ or $-COOR^4$, where R^4 represents a hydrogen atom, an alkyl, aryl, alkyl, or alkylaryl residue containing 1-10 carbon atoms, and where the compound of the general formula IIa is present, in the form of such compound, or in a form from

zoic acid. Other acids that can be used are described, for example, in *Fortschritte der Arzneimittelforschung*, vol. 10, pp. 224-225, Birkhäuser Verlag, Basel and Stuttgart, 1966, and *Journal of Pharmaceutical Sciences*, vol. 66, pp. 1-5 (1977).

Acid addition salts are normally obtained in a generally known way by mixing the free base or its solutions with the respective acid or its solutions in an organic solvent, for example, a lower alcohol, n-methanol, ethanol, n-propanol or isopropanol, or a lower ketone such as acetone, methyl ethyl ketone or methyl isobutyl ketone, or an ether such as diethyl ether, tetrahydrofuran or dioxane. Compositions of the abovementioned solvents may be used for improved crystallizing. In addition, physiologically compatible hydrous solutions of acid addition salts of the compound according to formula I may be produced in a hydrous acidic solution.

The acid addition salts of compounds of the general formula I can be converted into a free base in a generally known way, e.g. using alkalis or ion exchangers. Other salts can be obtained by reacting this free base with anorganic or organic acids, especially acids suited for forming pharmaceutically acceptable salts. These and other salts of the new compound, such as its picrate, may be used to purify the free base: the free base is converted into a salt, the salt is separated, and the base released from the salt again.

Another object of this invention are pharmaceuticals designed for oral, rectal, subcutaneous, intravenous or intramuscular applications that contain as an active ingredient, apart from the usual substrates and diluents, a compound according to the general formula I or its acid addition salt.

The pharmaceuticals of the invention are produced in a known way using the usual solid or liquid substrates or diluents and the common adjuvants used in pharmaceutical engineering and with an appropriate dosage depending on the intended mode of application. Preferred formulations are those forms suitable for oral administration, for example, tablets, film tablets, dragées, capsules, pills, powder, solutions, suspensions, or depot forms.

Consideration may be given also to parenteral formulations such as injection solutions. Suppositories represent another form of application.

Tablets may be obtained, for example, by intermixing the active substance with known adjuvants, for example, inert diluents such as dextrose, sugar, sorbitol, mannite, polyvinylpyrrolidone, binding agents such as maize starch or alginic acid, binders such as starch or gelatin, lubricants such as magnesium stearate or talcum and/or materials by which to produce a depot effect, such as carboxyl polymethylenes, carboxymethyl cellulose, cellulose acetate phthalate or polyvinyl acetate. Tablets may consist of several layers.

Dragées may be produced accordingly by coating cores manufactured in analogy to tablet manufacture using agents generally applied to dragée coating, for example, polyvinylpyrrolidone or shellac, Arabic gum, talcum, titanium dioxide, or sugar. The coating of the dragée may also consist of several layers in which the adjuvants mentioned in the paragraph on tablets can be used.

Solutions or suspensions containing the active agent of the invention may additionally contain flavour-enhancing substances such as saccharin, cyclamate or sugar, or aromatic substances such as vanillin or orange extract. They may also contain suspension-supporting adjuvants such as sodium carboxymethyl cellulose, or preservatives such as p-hydroxybenzoates. Capsules containing active substances may be produced, for example, by mixing the active sub-

stance with an inert substrate such as lactose or sorbitol, and encapsulating such mixture in gelatin capsules.

Appropriate suppositories may be made by mixing the active substance with the suitable substrates, such as neutral fats or polyethylene glycol and their derivatives.

The 11 β -substituted benzaldonins-extra-4,9-dienes of the invention are antigestagenic substances that show the same activity at the progesterone receptor as RU 486 (Mifepristone) (cf. table 1) and a superior in-vivo effect (cf. FIG. 1 and table 2) while at the same time having a clearly reduced antiglucocorticoid activity which has been proved by the diminished bonding to the gluco-corticoid receptor (cf. table 1) as well as by the decreased inhibition of enzyme induction in lines of cells which is by one power of ten lower (cf. FIGS. 2 and 3).

TABLE 1

Compound acc. to example	Receptor of selected substances listed in Examples 1 to 5		
	relative molar bonding affinity (RBA) [%] to		
	progesterone receptor (progesterone = 100%)	glucocorticoid receptor (dexamethasone = 100%)	oestrogen rec. (oestradiol = 100%)
1 (687)	302	78	<0.1
2	196	82	<0.1
3	236	73	<0.1
4	294	66	<0.1
5	90	32	<0.1
compared with			
RU 486	306	685	
(Mifepristone)			
ZK 96269	22	39	
(Onapristone)			

Selected antigestagens of the invention (J 687) produces significantly reduced uterine weights in the anovulatory cycle in guinea pigs at doses at which RU 486 increases uterine weights as compared with control animals.

This combination of properties of the antigestagen according to the invention promises superior inhibition of progesterone while at the same time reducing antiglucocorticoid activity.

This advantage is of particular relevance for indications that require excellent compatibility because of the duration of treatment. During the menstrual cycle, uterine weight is decisively influenced by the circulating oestrogen. Reduced uterine weights reflect an inhibition of this oestrogenic function. The inhibition of uterine weight during the menstrual cycle determined in guinea pigs is superior to RU 486 and points to (indirect) anti-oestrogenic properties of the compounds according to the invention. The respective effects promise the exertion of a particularly favourable influence on pathologically modified tissues in which oestrogens stimulate growth (endometriotic foci, myomas, mammary and genital carcinomas, benign prostatic hypertrophy).

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TABLE 2

Early abortion effect of RU 486 and J 867 (Example 1) in the rat after subcutaneous application from the 5th to 7th day of pregnancy (dose 0.2 ml/min/day in benzyl benzoate/mineral oil 1:4 v/v)

Group, substance	Dose (mg/mineral oil day)	complete gravidity inhibition ^c N*/N	%	ED 50** (mg/mineral oil day)
vehicle	—	0/13	0	—
RU 486	3.0	5/5	100	1.3
	1.0	2/5	40	
	0.3	0/5	0	
J 867	3.0	5/5	100	0.6
	1.0	5/5	100	
	0.3	0/5	0	

^aempty nest
N number of inseminated females
N* number of females not pregnant
^cgraphic determination

FIG. 1 compares the influence of antigestagen treatment of cyclic guinea pigs on uterine weights for J 867 and RU 486.

High doses of RU 486 (6 mg/24 hrs) reduce the uterine weights of the treated animals. A low dose of this substance, however, results in a slight gain in uterine weights. All doses of J 867 tested (1, 3, and 6 mg/24 hrs) inhibited uterine weights to a statistically significant extent.

FIG. 2 depicts the antiglucocorticoid effect produced by J 867 in the ZR 75/AGP-763 line of human mammary cells compared with that of RU 486.

In this cell line, dexamethasone induces the chloromphenicol acetyl transferase gene (CAT). This induction is inhibited by antiglucocorticoid substances. Surprisingly, J 867 inhibits CAT over a wide range of concentrations to a lesser extent than RU 486 (Mifepristone).

FIG. 3 compares the antiglucocorticoid effect of J 867 and RU 486 on hepatoma cells of rats using the TAT model.

In hepatoma cells of rats, dexamethasone stimulates the tyrosine amino transferase enzyme (TAT). This effect is inhibited by antiglucocorticoid activity. J 867 apparently has a clearly weaker antiglucocorticoid effect than RU 486.

The following examples explain the present invention.

EXAMPLES

Example 1

434 mg of 11 β -(4-formylphenyl)-17 β -methoxy-17 α -methoxymethyl-estra-4,9-diene-3-one are dissolved at room temperature in 8 ml of pyridine; then 65 mg of hydroxylamine hydrochloride are added, and the batch is agitated at 25° C. Another 5 mg of hydroxylamine hydrochloride are added after 2 hours. After 15 minutes, the solution is diluted with water, added with 1N of aqueous hydrochloric acid, and extracted with chloroform. The organic phase is washed with dilute HCl and water and dried above sodium sulfate and potassium carbonate. The solvent is evaporated under reduced pressure. Yield: 420 mg of crude product. After adding acetone, crystals precipitate that are filtered off by suction and recrystallized from isopropanol/CH₂Cl₂.

Yield: 305 mg of 11 β -(4-(hydroximinomethyl)phenyl)-17 β -methoxy-17 α -methoxymethyl-estra-4,9-diene-3-one.

Melting point: 118° C. with decomposition α_D^{20} +197° (CHCl₃)

IR spectrum in CHCl₃ (cm⁻¹): 3575, 3300 (OH); 1705 (C=NOH); 1649 (O=C—C=C—O=O); 1599 (phenyl)

UV spectrum in MeOH: λ_{max} =264 nm ϵ =20 366 λ_{min} =299 nm ϵ =20 228

¹H-NMR spectrum in CDCl₃ [δ , ppm]: 0.533 (s, 1H, H-18); 3.252 (s, 3H, 17 β -OCH₃); 3.393 (s, 3H, 17 α -CH₃OC H₃); 3.441–3.598 (m, 2H, ABX system of CH₂OR); 4.381 (d, 1H, J=6.9 Hz, H-11 α); 5.788 (s, 1H, H-4); 7.187–7.487 (m, 4H, AA'BB' system of aromatics protons); 8.05 (s, 1H, OH); 8.097 (s, 1H, CH=NOH)

MS m/e: 449.25509 C₂₉H₃₅NO₄ M⁺

Manufacturing of the parent compound:

Step A

50 g of 4-bromobenzaldehyde and 30 ml of o-triethyl formate are agitated for 5 hours at room temperature in 60 ml of methanol and 0.8 ml of thionyl chloride. After that, another 0.2 ml of thionyl chloride are added. The batch is poured into aqueous bicarbonate solution after 30 minutes and extracted with chloroform, washed with aqueous bicarbonate solution and water, dried above sodium sulfate, and concentrated by evaporation under reduced pressure. 68 g of 4-bromobenzaldehyde dimethyl ketal are obtained in the form of colourless oil.

0.2 ml of dibromomethane are added to 2.3 g of magnesium in 20 ml of anhydrous THF with argon as inert gas. When the reaction starts, 21.96 g of 4-bromobenzaldehyde dimethyl ketal in 70 ml of anhydrous THF are dripped in in such a way that the temperature does not rise above 40° C. After the whole amount has been added, the batch is agitated for 2 hours at 30° C., then cooled down to -10° C. 511 mg of CuCl are added. Agitation is continued at -30° C. for 15 more minutes. Then, a solution of 6 g of 3,3-dimethoxy-5 α , 10 α -epoxy-estr-9,11-en-17-on in 30 ml of anhydrous THF is dripped in. The batch is allowed to warm up to room temperature. The Grignard solution is decomposed using an aqueous solution of ammonium chloride. The product is isolated by extracting with acetic ester. The organic phase is washed neutrally and dried above sodium sulfate. After the solvent has been removed by distillation under reduced pressure, 19.7 g of crude product are obtained.

Chromatography using 300 g of silica gel and 20 g of aluminium oxide with a toluene/acetic ester gradient yields 7.38 g of 3,3-dimethoxy-11 β -(4-(dimethoxymethyl)phenyl)-5 β -hydroxy-estr-9-en-17-on in the form of a yellow foam. Step B

10.38 g of trimethyl sulfonium iodide and 7.64 g of (portioned) potassium tert. butanolate are added to 7.38 g of 3,3-dimethoxy-11 β -(4-(dimethoxymethyl)phenyl)-5 β -hydroxy-estr-9-en-17-on dissolved in 85 ml dimethylsulfonide using argon as inert gas. After 1.5 hours and cooling down to 0°–5° C., aqueous ammonium chloride solution is added. The sticky precipitate is extracted with CH₂Cl₂, washed neutrally, dried above sodium sulfate, and isolated in the form of brown resin after the solvent has been evaporated.

Yield: 8.63 g of 3,3-dimethoxy-11 β -(4-(dimethoxymethyl)phenyl)-17 β -spiro-1',2'-oxirane-estr-9-en-5 α -ol.

Step C

20 ml of a 3N sodium methylate solution are added to 8.63 g of 3,3-dimethoxy-11 β -(4-(dimethoxymethyl)phenyl)-17 β -spiro-1',2'-oxirane-estr-9-en-5 α -ol dissolved in 20 ml of methanol, and refluxed for 2–3 hours. The solvent is evaporated under reduced pressure, the remainder is taken up in CH₂Cl₂, and washed neutrally. The solution is dried above sodium sulfate and evaporated under reduced pressure.

Yield: 8.74 g of crude product in the form of a brown foam. Chromatography using 260 g of silica gel and 90 g of aluminium oxide in a toluene/acetic ester gradient yields

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Melting point: 241°-246° C. (acetone)

$\alpha_D^{25}+178^\circ$ (CHCl₃)

UV spectrum in MeOH: $\lambda_{max}=238$ nm $\epsilon=29$ 444 $\lambda_{min}=300$ nm $\epsilon=29$ 649

¹H-NMR spectrum in CDCl₃ [δ , ppm]: 0.474 (s, 3H, H-18); 3.245 (s, 3H, 17 β -OCH₃); 3.405 (s, 3H, 17 α -CH₂OC H₃); 3.406-3.545 (m, 2H, ABX system, 17 α -CH₂OCH₃); 4.413 (d, J=6.8 Hz, 1H, H-11 α); 5.797 (s, 1H, H-4); 7.264 (m, 5H, aromatic); 7.272, 7.293, 7.548, 7.575 (m, 4H, AA'BB' system of aromatics protons); 8.0 (s, 1H, C H=N-)

MS m/e: 431.24249 C₂₆H₃₃NO₃ M⁺-C₈H₉CNO+H₂O

Example 10

125 mg of 17 α -ethoxymethyl-11 β -(4-formylphenyl)-17 β -hydroxy-estra-4,9-diene-3-on are dissolved at room temperature in 2 ml of pyridine; then 20.2 mg of hydroxylamine hydrochloride are added, and the batch is agitated at 25° C. After 50 minutes, the solution is diluted with water, acetic ester is added, and the phases are separated. The organic phase is washed with dilute HCl and water and dried above sodium sulfate. The solvent is evaporated under reduced pressure.

127 mg of crude product in the form of a bright yellow foam are obtained that yield 62 mg of 17 α -ethoxymethyl-11 β -(4-(hydroxylaminomethyl)phenyl)-17 β -hydroxy-estra-4,9-diene-3-on in the form of a colourless foam after preparative thin-layer chromatography using silica gel 60 FF₂₅₄₊₃₆₆

$\alpha_D^{25}+226^\circ$ (CHCl₃)

UV spectrum in MeOH: $\lambda_{max}=265$ nm $\epsilon=22$ 696 $\lambda_{min}=299$ nm $\epsilon=21$ 960

¹H-NMR spectrum in CDCl₃ [δ , ppm]: 0.520 (s, 1H, H-18); 1.249 (t, 3H, J=7.2 Hz, 17 α -CH₂OCH₂CH₃); 3.228-3.609 (m, 4H, 2 $\times$ CH₂); 4.381 (d, 1H, J=7.2 Hz, H-11 α); 5.781 (s, 1H, H-4); 7.181, 7.209, 7.459, 7.486 (m, 4H, AA'BB' system of aromatics protons); 8.098 (s, 1H, C H=NOH).

MS m/e: 449.25540 C₂₆H₃₃NO₄ M⁺

Manufacturing of the parent compound
Step M

340 mg 3,3-dimethoxy-11 β -(4-(dimethoxymethyl)phenyl)-17 α -ethoxymethyl-estr-9-en-5 α ,17 β -diol (manufactured according to Step H in Example 7) are dissolved in 2.5 ml of acetone. 0.25 ml of water and 35 mg of 4-toluene sulfonic acid are added. After 1 hour, the batch is diluted with 10 ml of water, and 10 ml of acetic ester are added. The phases are separated. The aqueous solution is twice re-extracted, the organic solution is washed and dried above sodium sulfate. After evaporating the solvent, 300 mg of yellowish crystals remain.

200 mg of 17 α -ethoxymethyl-11 β -(4-formylmethyl)-17 β -hydroxy-estra-4,9-diene-3-on in the form of yellowish crystals are obtained after preparative thin-layer chromatography on silica gel 60 FF₂₅₄₊₃₆₆ with toluene/acetone (9:1).

Melting point: 144°-150° C. (acetone/hexane)

$\alpha_D^{25}+171^\circ$ (CHCl₃)

UV spectrum in MeOH: $\lambda_{max}=263$ nm $\epsilon=17$ 842 $\lambda_{min}=299$ nm $\epsilon=20$ 083

¹H-NMR spectrum in CDCl₃ [δ , ppm]: 0.512 (s, 1H, H-18); 1.249 (t, 3H, J=4.6 Hz, 17 α -CH₂OCH₂CH₃); 3.221-3.613 (m, 4H, 2 $\times$ CH₂); 4.447 (d, 1H, J=6.9 Hz, H-11 α); 5.799 (s, 1H, H-4); 7.361, 7.388, 7.788, 7.816 (m, 4H, AA'BB' system of aromatics protons); 9.972 (s, 1H, C H=O).

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Example 11

Measurement of bonding affinity for receptors

Receptor bonding affinity was determined by competitive bonding of a specifically binding ³H labelled hormone (tracer) and the compound to be tested to receptors in the cytosol from animal target organs. It was tried to obtain receptor saturation and a balanced reaction. The following incubation conditions were selected:

Progesterone receptor: uterine cytosol of the estradiol-primed rabbit, kept at -30° C. in TED buffer (20 mM Tris/HCl, pH 7.4; 1 mM ethylene diamine tetraacetate, 2 mM dithio threitol) with 250 mM of saccharose. Tracer: ³H-ORG 2058, 5 nM; reference substance: progesterone.

Glucocorticoid receptor: thymus cytosol of the adrenalectomized rat, thymus kept at -30° C., buffer: TED. Tracer: ³H-dexamethasone, 20 nM; reference substance: dexamethasone.

Oestrogen receptor: uterine cytosol of the immature rabbit, kept at -30° C. in TED buffer with 250 mM of saccharose. Tracer: ³H-ethinyl estradiol, 3 nM; reference substance: 17 β -estradiol.

After an incubation period of 18 hours at 0°-4° C., bonded and free steroid was separated by mixing in active carbon/dextrane (1%/0.1%), centrifuging off and measuring the bonded ³H activity in the supernatant.

The IC₅₀ for the compound to be tested and for the reference substance were determined from measurements in series of concentrations. The quotient of both values ($\times 100\%$) is the relative molar bonding affinity.

Example 12

Inhibition of early gravidity in the rat

Female rats are mated in the pro-oestrus. If semen is found in the vaginal smear on the next day, this day is counted as day 1 (=d1) of the gravidity. Treatment with the test substance or vehicle is applied on d5-d7, autopsy is carried out on d9. The substances are injected subcutaneously in 0.2 ml of vehicle (benzyl benzoate/castor oil 1+4). The rate of fully inhibited gravidities found in various groups can be seen from table 1. An inhibition capability of nidation was found for J 867 to be superior by a factor of 3 as compared to RU 486.

Example 13

Treatment of female guinea pigs with antigestagen

Treatment of adult female guinea pigs from day 10 to day 18 of the cycle (autopsy). Administration of the specified doses using subcutaneous osmotic pumps (Type 2 ML1 ALZET). Vehicle: 2.0 ml propylene glycol/24 hrs.

Example 14

Antiglucocorticoid effect of J867 in the ZR75/AGP-763 line of human mammary cells

The cell culture experiments were carried out in RPMI 1640 added with 10% fetal calf serum (FCS) using an incubator cabinet containing 95% air and 5% CO₂ at 37° C. The cells were spread in 60 mm Petri dishes. The medium of the confluent cells was replaced by a medium containing 5% FCS (treated with dextrane coated charcoal, DCC). Dexamethasone at a concentration of 10⁻⁷M in ethanol (0.2%; v/v) was added to induce CAT. The stimulated cells were harvested 16 hours later by producing a cell extract with a cell lysis buffer. CAT was determined using a Boehringer ELISA according to the instructions for quantitative CAT determination of transfected cells.

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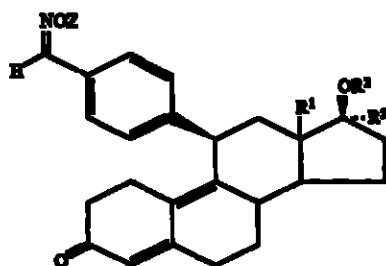
Example 15

Antigluccorticoid effect of J867 in hepatomatous cells of rats using the TAT model

The cell cultures were treated in DMEM under essentially the same conditions as in Example 14. The cells were spread over 24 well plates for the experiments. Substance was added to the confluent hepatomatous cells in 0.2% (v/v) ethanol for 16 hours. After the cells were carefully harvested using a scraper and a cell extract obtained using ultrasonic waves, TAT was determined according to Diamondstone.

What we claim is:

1. 11 β -benzaldehyde-estra-4,9-diene-derivatives of the general formula I:



Formula I

wherein

R¹ is selected from the group consisting of a hydrogen atom or alkyl residue containing 1-6 carbon atoms,

R² is selected from the group consisting of a hydrogen atom, an alkyl, aryl, aralkyl, or alkylaryl group containing 1-10 carbon atoms, an acyl residue containing 1-10 carbon atoms, or a residue —CONHR⁴ or —COOR⁴,

where R⁴ is selected from the group consisting of a hydrogen atom, an alkyl, aryl, aralkyl, or alkylaryl residue containing 1-10 carbon atoms,

R³ is selected from the group consisting of a hydrogen atom, an alkyl, aryl, aralkyl, or alkylaryl group containing 1-10 carbon atoms,

a residue —(CH₂)_n—CH₂X,

where n=0, 1, or 2, X is selected from the group consisting of a fluorine, chlorine, bromine, or iodine atom, a cyano, azido, or rhodano group, a residue OR⁵ or SR⁵,

R⁵ being a hydrogen atom, an alkyl, aryl, aralkyl, or alkylaryl residue containing 1-10 carbon atoms, or an acyl residue containing 1-10 carbon atoms,

a residue OR⁶,

in which R⁶ has the meaning specified above,

a residue —(CH₂)_p—CH=CH(CH₂)_q—R⁶,

where q=0, 1, 2, or 3 and p=0, 1, or 2, and R⁶ is selected from the group consisting of a hydrogen atom, an alkyl, aryl, aralkyl, or alkylaryl group containing 1-10 carbon atoms, a hydroxy group, an alkoxy or acyloxy group containing 1-10 carbon atoms,

a residue —(CH₂)_q—C≡CR⁷,

where q=0, 1, or 2, and R⁷ is selected from the group consisting of a hydrogen atom, a fluorine, chlorine, bromine, or iodine atom, an alkyl, aryl, aralkyl, or alkylaryl residue containing 1-10 carbon atoms, or an acyl residue containing 1-10 carbon atoms,

Z is selected from the group consisting of a hydrogen atom, an alkyl, aryl, aralkyl, or alkylaryl residue containing 1-10 carbon atoms, or an acyl residue containing 1-10 carbon atoms, a residue

—CONHR⁴ or —COOR⁴,

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where R⁴ is selected from the group consisting of a hydrogen atom, an alkyl, aryl, aralkyl, or alkylaryl residue containing 1-10 carbon atoms, or an alkaline or alkaline-earth metal atom, and pharmaceutically acceptable salts thereof;

with the exception of compounds wherein

R² is —CH₃, R³ is —CH₂—O—CH₃, and Z is —CO—CH₃, —CO—O—C₂H₅, —CO—NH-phenyl, —CO—NH—C₂H₅, —CO—C₂H₅, —CO-phenyl or —CH₃.

2. Compounds according to claim 1, wherein R¹ is selected from the group consisting of a methyl and an ethyl group.

3. Compounds according to claim 1 or 2, characterized in that R² is selected from the group consisting of an alkyl group containing 1-6 carbon atoms, an acyl residue containing 1-6 carbon atoms, or

a residue —CONHR⁴ or —COOR⁴,

where R⁴ is selected from the group consisting of a hydrogen atom or an alkyl or aryl residue containing 1-6 carbon atoms.

4. Compounds according to claim 1 or 2, characterized in that R³ is selected from the consisting of an alkyl group containing 1-6 carbon atoms.

5. Compounds according to claim 1, characterized in that R³ is selected from the group consisting of a residue —(CH₂)_n—CH₂X,

where n=0, 1, or 2, X is selected from the group consisting of a fluorine, chlorine, bromine, or iodine atom, a cyano, azido, or rhodano group, a residue OR⁵ or SR⁵, wherein

R⁵ is selected from the group consisting of an alkyl residue containing 1-6 carbon atoms, or an acyl residue containing 1-6 carbon atoms.

6. Compounds according to claim 1 or 2, characterized in that R³ is selected from the group consisting of a residue OR⁵,

R⁵ is selected from the group consisting of an alkyl residue containing 1-6 carbon atoms, or an acyl residue containing 1-6 carbon atoms.

7. Compounds according to claim 1 or 2, characterized in that R³ is selected from the group consisting of a residue —(CH₂)_p—CH=CH(CH₂)_q—R⁶,

where q=0, 1, 2 or 3 and p=0, 1, or 2 and R⁶ is selected from the group consisting of an alkyl group containing 1-6 carbon atoms, an alkoxy or acyloxy group containing 1-6 carbon atoms.

8. Compounds according to claim 1 or 2, characterized in that R³ is selected from the group consisting of a residue —(CH₂)_q—C≡CR⁷,

where q=0, 1, or 2 and R⁷ is selected from the group consisting of an alkyl residue containing 1-6 carbon atoms, or an acyl residue containing 1-6 carbon atoms.

9. Compounds according to claim 1 or 2, characterized in that Z is selected from the group consisting of an alkyl residue containing 1-6 carbon atoms, an acyl residue containing 1-6 carbon atoms, a residue —CONHR⁴ or —COOR⁴,

where R⁴ is selected from the group consisting of a hydrogen atom, an alkyl or an aryl residue containing 1-6 carbon atoms.

10. Compounds according to claim 1, selected from the group consisting of:

11 β -[4-(hydroxymethyl)phenyl]-17 β -hydroxy-17 α -methoxymethyl-estra-4,9-diene-3-on,

11 β -[4-(hydroxymethyl)phenyl]-17 β -hydroxy-17 α -ethoxymethyl-estra-4,9-diene-3-on,

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R^3 is selected from the group consisting of a hydrogen atom, an alkyl, aryl, aralkyl, or alkylaryl residue containing 1-10 carbon atoms,

a residue $-(CH_2)_n-CH_2X$,

where $n=0, 1$, or 2 , X is selected from the group consisting of a hydrogen atom, an alkyl, aryl, aralkyl, or alkylaryl residue containing 1-10 carbon atoms, a fluorine, chlorine, bromine, or iodine atom, a cyano, azido, or rhodano group, a residue OR^5 or SR^5 ,

R^5 is selected from the group consisting of a hydrogen atom, an alkyl, aryl, aralkyl, or alkylaryl residue containing 1-10 carbon atoms, or an acyl residue containing 1-10 carbon atoms,

a residue OR^6 ,

in which R^6 has the meaning specified above,

a residue $-(CH_2)_o-CH=CH(CH_2)_p-R^6$,

where $o=0, 1, 2$, or 3 and $p=0, 1$, or 2 , and R^6 is selected from the group consisting of a hydrogen atom, an alkyl, aryl, aralkyl, or alkylaryl group containing 1-10 carbon atoms, a hydroxyl group, an alkoxy or acyloxy group containing 1-10 carbon atoms,

a residue $-(CH_2)_q-O-CR^7$,

where $q=0, 1$, or 2 , and R^7 is selected from the group consisting of a hydrogen atom, a fluorine, chlorine,

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bromine, or iodine atom, an alkyl, aryl, aralkyl, or alkylaryl residue containing 1-10 carbon atoms, or an acyl residue containing 1-10 carbon atoms,

with a compound of the general formula IIa



Formula IIa

where Y is selected from the group consisting of a hydrogen atom, an alkyl residue containing 1-10 carbon atoms, an acyl residue containing 1-10 carbon atoms, or a residue



where R^4 is selected from the group consisting of a hydrogen atom, an alkyl, aryl, aralkyl, or alkylaryl residue containing 1-10 carbon atoms.

14. Pharmaceutical compositions, characterized in that they contain at least one compound according to claim 1.

15. A pharmaceutical composition, comprising a pharmaceutically effective concentration of a compound according to claim 1, or salts or mixtures thereof, in a pharmaceutically acceptable carrier.

* * * * *

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Jensapharm GmbH, 07745 Jena, DE

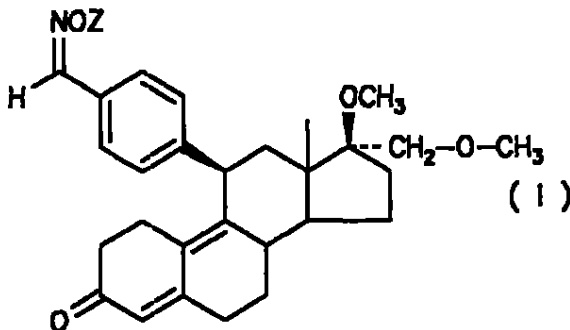
⑦② Vertreter:
Weblat, W., Dipl.-Chem. Dr.-Ing. Dr. jur., Pat.-Anw.,
14129 Berlin

⑦③ Erfinder:
Schubert, Gerd, Dr., 07743 Jena, DE; Kaufmann,
Günther, Dr., 07743 Jena, DE; Soback, Lothar, Dr.,
07743 Jena, DE; Oettel, Michael, Prof. Dr., 07743
Jena, DE; Elger, Walter, Dr., 14195 Berlin, DE;
Kurischko, Anatoli, Dr., 07745 Jena, DE

Prüfungsantrag gem. § 44 PatG ist gestellt

⑥ Neue 11-Benzaldoxim-17 β -methoxy-17 α -methoxymethyl- α -estradien-Derivate, Verfahren zu ihrer Herstellung und diese Verbindungen enthaltende Arzneimittel

Beschrieben sind neue 11-Benzaldoxim- α -estradien-Derivate der allgemeinen Formel I



und deren pharmazeutisch annehmbare Salze, ein Verfahren zu ihrer Herstellung und diese Verbindungen enthaltende Arzneimittel.
Die beschriebenen Verbindungen zeigen starke antigestagene Wirkungen bei geringerer glucocorticoide Aktivität.

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Die folgenden Angaben sind den vom Anmelder eingereichten Unterlagen entnommen
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Beschreibung

Die Erfindung betrifft neue 11-Benzaldoxim-estradien-Derivate, Verfahren zu ihrer Herstellung und diese Verbindungen enthaltende Arzneimittel.

11 β -substituierte Phenyl-estratriene sind bereits bekannt. Die Herstellung von 11 β -Aryl-17 α -propinyl-estra-4,9-dienen ist z. B. in der Patentschrift EP 057 115, die Umsetzung von 11 β -(4-Formylphenyl)-estra-4,9-dien-3-onen mit Hydroxylaminen in der Patentschrift DE 35 04 421 bereits beschrieben. In dem angegebenen Verfahren wird sowohl die 11 β -Formylphenylgruppe als auch die 3-Ketogruppe oximiert. Außerdem entstehen am C-3 syn- und anti-Isomere. Über die Wirkung der beschriebenen Verbindungen ist bisher nichts bekannt.

Progesteron wird während des Zyklus und in der Gravidität in großen Mengen vom Ovar und der Plazenta sezerniert. Seine regulatorische Bedeutung ist vermutlich nicht in allen Aspekten geklärt.

Gesichert ist, daß Progesteron im Zusammenwirken mit Oestrogenen die zyklischen Veränderungen der Uterusschleimhaut im Menstruationszyklus und der Gravidität bewirkt. Unter dem Einfluß erhöhter Progesteronspiegel nach der Ovulation wird die Uterusschleimhaut in einen Zustand überführt, der die Einnistung eines Embryos (Blastozyste) zuläßt. Die Erhaltung der Gewebe, in denen sich der wachsende Embryo ausbreitet, ist ebenfalls progesteronabhängig.

In der Gravidität findet eine dramatische Veränderung der muskulären Funktion des Uterus statt. Der gravide Uterusmuskel reagiert stark abgeschwächt oder gar nicht auf hormonale und mechanische Reize, die außerhalb der Gravidität Wehen auslösen. Es kann kein Zweifel daran bestehen, daß hierbei Progesteron eine Schlüsselrolle spielt, obwohl in manchen Phasen der Gravidität, z. B. unmittelbar vor der Geburt, eine hohe Reaktionsbereitschaft bei extrem hohen Blutspiegeln von Progesteron besteht.

Andere typische Vorgänge der Schwangerschaft sind ebenfalls Ausdruck der sehr hohen Progesteronspiegel. Der Aufbau der Brustdrüsen und der feste Verschluss des Muttermundes bis in die Nähe des Geburtstermins sind hierfür Beispiele.

Progesteron ist in subtiler Weise an der Steuerung von Ovulationsvorgängen beteiligt. Es ist bekannt, daß Progesteron in hohen Dosierungen antiovulatorische Eigenschaften besitzt. Diese resultieren aus einer Hemmung der hypophysären Gonadotropinsekretion, die Voraussetzung für die Reifung eines Follikels und dessen Ovulation ist. Andererseits ist erkennbar, daß die vergleichsweise geringe Progesteronsekretion des reifenden Follikels eine aktive Rolle für die Vorbereitung und Auslösung der Ovulation spielt. Hierbei spielen hypophysäre Mechanismen (zeitlich begrenzter sog. positiver feed back des Progesterons auf Gonadotropinsekretion) erkennbar eine wichtige Rolle (Loutradie, D.; Human Reproduction 6, 1991, 1238—1240).

Weniger gut analysiert sind Funktionen des Progesterons im reifenden Follikel und Gelbkörper selbst, an deren Existenz kein Zweifel besteht. Letztlich sind auch hier stimulierende und hemmende Effekte auf endokrine Follikel- und Gelbkörperfunktion anzunehmen.

Eine bedeutende Rolle des Progesterons und der Progesteronrezeptoren ist auch in pathophysiologischen Prozessen anzunehmen. Progesteronrezeptoren sind in Endometrioseherden, aber auch in Tumoren des Uterus, der Mamma und des ZNS (Meningeome) nachgewiesen. Die Rolle dieser Rezeptoren für das Wachstumsverhalten dieser pathologisch relevanten Gewebe ist nicht notwendigerweise an das Vorliegen von Progesteronspiegeln im Blut gebunden. Es ist erweisen, daß Substanzen, die als Progesteronantagonisten charakterisiert sind, RU 486 = Mifepriston (EP-0 057 115) und ZK 98299 = Onapriston (DE-OS-35 04 421) in diesen Geweben auch dann tiefgreifende Funktionsänderungen auslösen, wenn vernachlässigbar geringe Progesteronspiegel im Blut vorliegen. Es erscheint möglich, daß hierbei Änderungen von Transkriptionswirkungen des nicht von Progesteron besetzten Progesteronrezeptors durch die Antagonisten eine wichtige Rolle spielen (Chwalisz, K. et al, Endocrinology, 129, 317—322, 1991).

Die Wirkungen von Progesteron in Geweben der Genitalorgane und anderen Geweben erfolgen durch Interaktion mit dem Progesteronrezeptor. In der Zelle bindet sich Progesteron mit hoher Affinität an seinen Rezeptor. Hierdurch werden Veränderungen des Rezeptorproteins bewirkt: Konformationsveränderungen, Dimerisierung von 2 Rezeptoreinheiten zu einem Komplex, Entblößung der DNA-Bindungsstelle des Rezeptors durch Abdissoziation eines Proteins (HSP 90), Bindung an Hormon-responsible Elemente der DNA. Letztlich wird die Transkription bestimmter Gene reguliert. (Gronemeyer, H. et al, J. Steroid Biochem. Molec. Biol. 41, 3—8, 1992).

Die Wirkung von Progesteron oder von Progesteronantagonisten ist nicht nur von ihrer Konzentration im Blut abhängig. Die Konzentration von Rezeptoren in der Zelle ist ebenfalls stark reguliert. Oestrogene stimulieren die Synthese von Progesteronrezeptoren in den meisten Geweben. Progesteron hemmt die Synthese von Oestrogenrezeptoren und diejenige seines eigenen Rezeptors. Vermutlich sind es diese und andere interaktive Beziehungen zwischen Oestrogenen und Gestagenen, die erklären können, warum Gestagene und Antigestagene oestrogenabhängige Vorgänge beeinflussen können ohne daß sie vom Oestrogenrezeptor gebunden werden. Diese Beziehungen sind naturgemäß von großer Bedeutung für die therapeutische Anwendung von Antigestagenen. Diese Substanzen erscheinen geeignet, gezielt in Reproduktionsvorgänge der Frau einzugreifen, z. B. postovulatorisch, um die Nidation zu verhindern, in der späteren Gravidität, um Reaktionsbereitschaft des Uterus für Prostaglandine und Oxytocin zu erhöhen oder um eine Eröffnung und Erweichung ("Reifung") der Cervix zu erreichen.

Antigestagene hemmen bei verschiedenen subhumanen Primatenspezies die Ovulation. Der Mechanismus dieser Wirkung ist nicht eindeutig geklärt. Diskutiert werden neben einer Hemmung der Gonadotropinsekretion auch ovarielle Mechanismen durch Störung para- und autokriner Funktionen des Progesteron im Ovar.

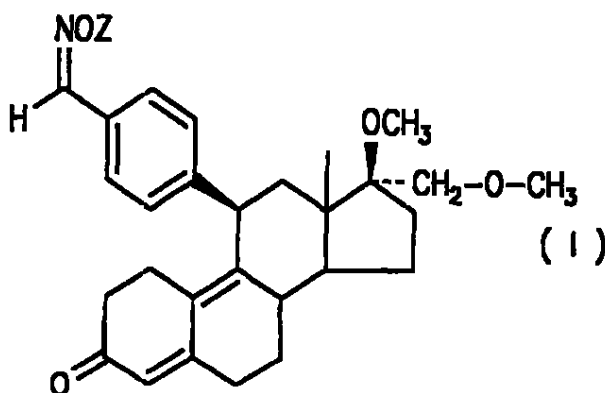
Antigestagene haben die Fähigkeit, die Effekte von Oestrogenen zu modulieren oder abzuschwächen, obwohl sie selbst überwiegend keine Affinität zum Oestrogenrezeptor auf cytoplasmatischer Ebene besitzen und obwohl sie einen Anstieg der Oestrogenrezeptorkonzentration bewirken können. Von entsprechenden Effekten

kann in Endometrioseherden bzw. in Tumorgewebe, das mit Oestrogen- und Progesteronrezeptoren ausgestattet ist, eine günstige Beeinflussung von Krankheitszuständen erwartet werden. Besondere Vorteile für die günstige Beeinflussung von Krankheitszuständen wie Endometriose könnten dann gegeben sein, wenn zu den Hemmeffekten eines Antigestagens durch die Wirkung im Gewebe eine Hemmung der Ovulation treten würde. Mit der Hemmung der Ovulation würde auch ein Teil der ovariellen Hormonproduktion und damit der auf diesen Anteil entfallende Stimulationseffekt auf das pathologisch veränderte Gewebe entfallen. Es wäre wünschenswert, bei Vorliegen einer schweren Endometriose die Ovulation zu hemmen und die sonst ständig im Umbau befindlichen Gewebe des Genitaltraktes reversibel in einen ruhenden Zustand zu versetzen.

Auch für die Kontrazeption wird ein Verfahren diskutiert, bei dem eine Antigestagenbehandlung die Ovulation unterdrückt, und durch eine anschließende Gestagenbehandlung die sekretorische Transformation des Endometriums induziert wird, so daß aus Behandlungstagen mit Antigestagenen und Gestagenen und behandlungsfreien Tagen ein ca. 28-tägiger Zyklus mit regelmäßigen Entzugsblutungen resultiert (Baulieu, E.E., Advances in Contraception 7, 345-51, 1991).

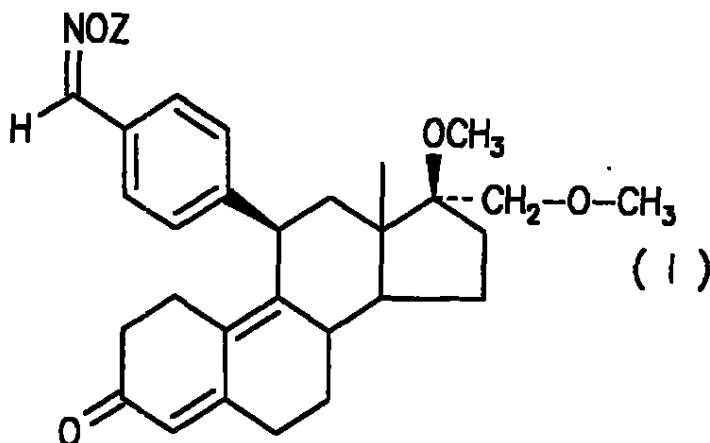
Antigestagene können unterschiedliche hormonale und antihormonale Eigenschaften besitzen. Von besonderer therapeutischer Relevanz sind hierbei antiglucocorticoide Eigenschaften. Diese sind für therapeutische Anwendungen, bei denen die Hemmung der Progesteronrezeptoren im Vordergrund der Therapie steht, nachteilig, da sie bei den therapeutisch erforderlichen Dosierungen unerwünschte Nebenwirkungen verursachen, die Applikation einer therapeutisch sinnvollen Dosis verhindern, oder zum Abbruch der Behandlung führen können. Die teilweise oder vollständige Reduktion antiglucocorticoider Eigenschaften ist eine wichtige Voraussetzung für die Therapie mit Antigestagenen, insbesondere für diejenigen Indikationen, die eine über Wochen oder Monate dauernde Behandlung erfordern.

Aufgabe der vorliegenden Erfindung ist es, neue 11 β -Benzaldoximestra-4,9-dien-Derivate der allgemeinen Formel



und ihre pharmazeutisch annehmbaren Salze sowie ein Verfahren zu ihrer Herstellung zur Verfügung zu stellen. Eine weitere Aufgabe ist es, Arzneimittel, die eine Verbindung der allgemeinen Formel I oder deren pharmazeutisch annehmbares Salz erhalten, zur Verfügung zu stellen.

In der allgemeinen Formel I,



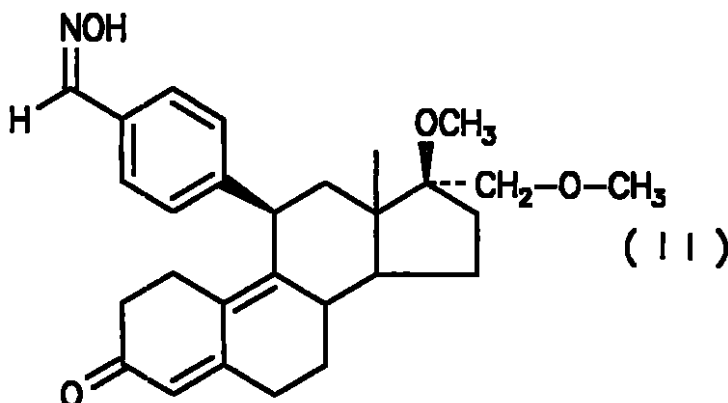
steht Z für -CO-CH₃, -CO-O-C₂H₅, -CO-NH-Phenyl, -CO-NH-C₂H₅, -CO-C₂H₅, -CH₃ oder -CO-Phenyl.

Bevorzugte erfindungsgemäße Verbindungen sind:

11 β -(4-(Acetoximinoethyl)phenyl)-17 β -methoxy-17 α -methoxymethyl-estra-4,9-dien-3-on,

11β-[4-[(Ethoxycarbonyl)oximinomethyl]phenyl]-17β-methoxy-17α-methoxymethyl-estra-4,9-dien-3-on,
 11β-[4-[(Ethylaminocarbonyl)oximinomethyl]phenyl]-17β-methoxy-17α-methoxymethyl-estra-4,9-dien-3-on,
 17β-Methoxy-17α-methoxymethyl-11β-[4-[(phenylaminocarbonyl)oximinomethyl]phenyl]-estra-4,9-dien-3-on,
 11β-[4-(Propionyloximinomethyl)phenyl]-17β-methoxy-17α-methoxymethyl-estra-4,9-dien-3-on,
 11β-[4-(Methyloximinomethyl)phenyl]-17β-hydroxy-17α-methoxymethyl-estra-4,9-dien-3-on und
 11β-[4-(Benzoyloximinomethyl)phenyl]-17β-hydroxy-17α-methoxymethyl-estra-4,9-dien-3-on.

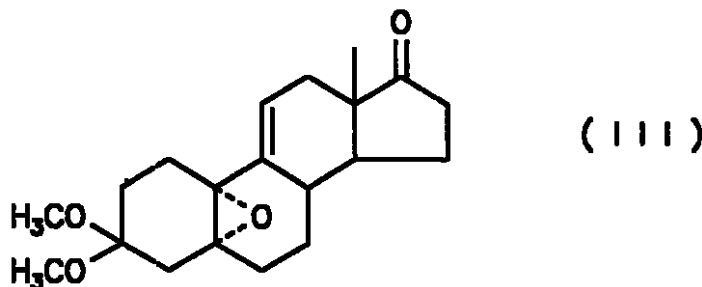
Die Erfindung betrifft ferner ein Verfahren zur Herstellung der Verbindungen nach der allgemeinen Formel I und deren pharmazeutisch annehmbaren Salze, das dadurch gekennzeichnet ist, daß man eine Verbindung der allgemeinen Formel II,



verestert oder verethert und gegebenenfalls die erhaltene Verbindung in ein Salz überführt.

Die Herstellung von Verbindungen der allgemeinen Formel I mittels Veresterung, Veretherung oder Urethan-Bildung kann in an sich bekannter Weise mit Acylierungsmitteln wie Säureanhydriden oder Säurechloriden in Gegenwart von Basen, vorzugsweise Pyridin, die Veretherung mit Methyljodid in Gegenwart von Basen, vorzugsweise Kalium-tert.-butanolat oder mit Diazomethan in Methanol wird die Urethan-Bildung durch Reaktion mit Alkyl- oder Arylisocyanaten in inerten Lösungsmitteln, vorzugsweise Toluol oder durch Reaktion von Carbamoylchloriden in Gegenwart von Basen, vorzugsweise Triethylamin durchgeführt werden.

Die Herstellung der Ausgangsverbindung der allgemeinen Formel II erfolgt aus dem 5α,10α-Epoxid III



[vgl. z. B. Nédélec Bull. Soc. chim. France (1970), 2548].

Die Einführung des Phenylrestes in die 11β-Stellung unter Ausbildung einer Δ⁹(10),5α-Hydroxy-Struktur IV wird durch Cu(I)-Salz katalysierte Grignard-Reaktion (Tetrahedron Letters 1979, 2051) mit einem p-Brombenzaldehydketal, vorzugsweise dem p-Brombenzaldehyddimethylketal bei Temperaturen zwischen 0°C und 30°C erreicht.

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zenssäure, Salicylsäure, Adipinsäure und Benzoesäure. Weitere verwendbare Säuren sind beispielsweise in Fortschritte der Arzneimittelforschung, Bd. 10, Seiten 224—225, Birkhäuser Verlag, Basel und Stuttgart, 1966, und Journal of Pharmaceutical Sciences, Bd. 66, Seiten 1—5 (1977) beschrieben.

Die Säureadditionssalze werden in der Regel in an sich bekannter Weise durch Mischen der freien Base oder deren Lösungen mit der entsprechenden Säure oder deren Lösungen in einem organischen Lösungsmittel, beispielsweise einem niederen Alkohol wie Methanol, Ethanol, n-Propanol oder Isopropanol oder einem niederen Keton wie Aceton, Methylethylketon oder Methylisobutylketon oder einem Ether wie Diethylether, Tetrahydrofuran oder Dioxan, erhalten. Zur besseren Kristallabscheidung können auch Mischungen der genannten Lösungsmittel verwendet werden. Darüber hinaus können physiologisch verträgliche wäßrige Lösungen von Säureadditionssalzen der Verbindung der Formel I in einer wäßrigen Säurelösung hergestellt werden.

Die Säureadditionssalze der Verbindungen der allgemeinen Formel I können in an sich bekannter Weise, z. B. mit Alkalien oder Ionenaustauschern, in die freie Base überführt werden. Von der freien Base lassen sich durch Umsetzung mit anorganischen oder organischen Säuren, insbesondere solchen, die zur Bildung von therapeutisch verwendbaren Salzen geeignet sind, weitere Salze gewinnen. Diese oder auch andere Salze der neuen Verbindung, wie z. B. das Pikrat, können auch zur Reinigung der freien Base dienen, indem man die freie Base in ein Salz überführt, dieses abtrennt und aus dem Salz wiederum die Base freisetzt.

Gegenstand der vorliegenden Erfindung sind auch Arzneimittel zur oralen, rektalen, subcutanen, intravenösen oder intramuskulären Applikation, die neben üblichen Träger- und Verdünnungsmitteln eine Verbindung der allgemeinen Formel I oder deren Säureadditionssalz als Wirkstoff enthalten.

Die Arzneimittel der Erfindung werden mit den üblichen festen oder flüssigen Trägerstoffen oder Verdünnungsmitteln und den üblicherweise verwendeten pharmazeutisch-technischen Hilfsstoffen entsprechend der gewünschten Applikationsart mit einer geeigneten Dosierung in bekannter Weise hergestellt. Die bevorzugten Zubereitungen bestehen in einer Darreichungsform, die zur oralen Applikation geeignet ist. Solche Darreichungsformen sind beispielsweise Tabletten, Filmtabletten, Dragees, Kapseln, Pillen, Pulver, Lösungen oder Suspensionen oder Depotformen.

Selbstverständlich kommen auch parenterale Zubereitungen wie Injektionslösungen in Betracht. Weiterhin sollen als Zubereitungen beispielsweise auch Suppositorien genannt.

Entsprechende Tabletten können beispielsweise durch Mischen des Wirkstoffs mit bekannten Hilfsstoffen, beispielsweise inerten Verdünnungsmitteln wie Dextrose, Zucker, Sorbit, Mannit, Polyvinylpyrrolidon, Sprengmitteln wie Maisstärke oder Alginsäure, Bindemitteln wie Stärke oder Gelantine, Gleitmitteln wie Magnesiumstearat oder Talk und/oder Mitteln zur Erzielung eines Depoteffektes wie Carboxypolymethylen, Carboxymethylcellulose, Celluloseacetatphthalat oder Polyvinylacetat, erhalten werden. Die Tabletten können auch aus mehreren Schichten bestehen.

Entsprechend können Dragees durch Überziehen von analog den Tabletten hergestellten Kernen mit üblicherweise in Drageeüberzügen verwendeten Mitteln, beispielsweise Polyvinylpyrrolidon oder Schellack, Gummiarabicum, Talk, Titandioxid oder Zucker, hergestellt werden. Dabei kann auch die Drageehülle aus mehreren Schichten bestehen, wobei die oben bei den Tabletten erwähnten Hilfsstoffe verwendet werden können.

Lösungen oder Suspensionen mit dem erfindungsgemäßen Wirkstoff können zusätzlich geschmacksverbessernde Mittel wie Saccharin, Cyclamat oder Zucker sowie z. B. Aromastoffe wie Vanillin oder Orangenextrakt enthalten. Sie können außerdem Suspendierhilfsstoffe wie Natriumcarboxymethylcellulose oder Konservierungstoffe wie p-Hydroxybenzoate enthalten. Wirkstoffe enthaltende Kapseln können beispielsweise hergestellt werden, indem man den Wirkstoff mit einem inerten Träger wie Milchzucker oder Sorbit mischt und in Gelatine-kapseln einkapselt.

Geeignete Suppositorien lassen sich beispielsweise durch Vermischen mit dafür vorgesehenen Trägermitteln wie Neutralfetten oder Polyäthylenglykol bzw. deren Derivaten herstellen.

Die erfindungsgemäßen 11 β -substituierten Benzaldoxime-4,9-diene sind antigestagen wirkende Substanzen, die bei überlegener Wirkung in vivo (vgl. Tab. 2) eine im Vergleich zu RU 486 deutlich reduzierte antiglucocorticoide Aktivität besitzen, nachgewiesen durch die verminderte Glucocorticoid-Rezeptorbindung (vgl. Tab. 1)

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Tabelle 2

Frühabortive Wirkung von RU 486 und J 914 (Beispiel 1) und J 900 (Beispiel 2) bei der Ratte nach subkutaner Applikation vom 5.-7. Graviditätstag (Applikation 0,2 ml/Tier/Tag in Benzylbenzoat/Rizinusöl [1 + 4 v/v])

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Gruppe, Substanz	Dosis (mg/Tier/Tag)	komplette Graviditätssthemmung ⁺		ED 50 ++ mg/Tier/Tag)
		N* /N	%	
Vehikel	-	0/25	0	-
RU 486	3,0	5/5	100	
	1,0	2/5	40	1,1
	0,3	0/5	0	
J 900	1,0	9/10	90	0,6
	0,3	0/5	0	
J 914	3,0	5/5	100	
	1,0	7/10	70	0,6
	0,3	1/5	20	
	0,1	0/6	0	

+ - leere Uteri;
N - Zahl der gesamten Weibchen;
N* - Zahl der nichtgraviden Weibchen;
++ - graphische Bestimmung

Die folgenden Beispiele erläutern die Erfindung

Beispiele

Beispiel 1

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180 mg 11β-[4-(Hydroximinomethyl)phenyl]-17β-methoxy-17α-methoxymethyl-estra-4,9-dien-3-on werden in 5 ml Acetanhydrid/Pyridin (1 : 1) acetyliert. Nach Zugabe von Wasser wird dreimal mit Essigester extrahiert, die organische Phase mit verd. Salzsäure und Wasser gewaschen, über Natriumsulfat getrocknet und unter vermindertem Druck eingeengt. Man erhält 172 mg Rohprodukt, das durch präparative Schichtchromatographie an Kieselgel PF₂₄₅+388 mit dem Laufmittelgemisch Toluol/Aceton 4 : 1 gereinigt wird.
Es werden 115 mg 11β-[4-(Acetyloximinomethyl)phenyl]-17β-methoxy-17α-methoxymethyl-estra-4, 9-dien-3-on erhalten. Das Produkt kristallisiert aus Essigester.
Schmelzpunkt: 115-120°C (Essigester) α_D = + 218° (CHCl₃)
IR-Spektrum in KBr (cm⁻¹): 1754 (OAc); 1654 (C=C-C-C-C=O) 1602 (Phenyl)
UV-Spektrum in MeOH:
λ_{max} = 271 nm ε = 28 157
λ_{max} = 297 nm ε = 26 369

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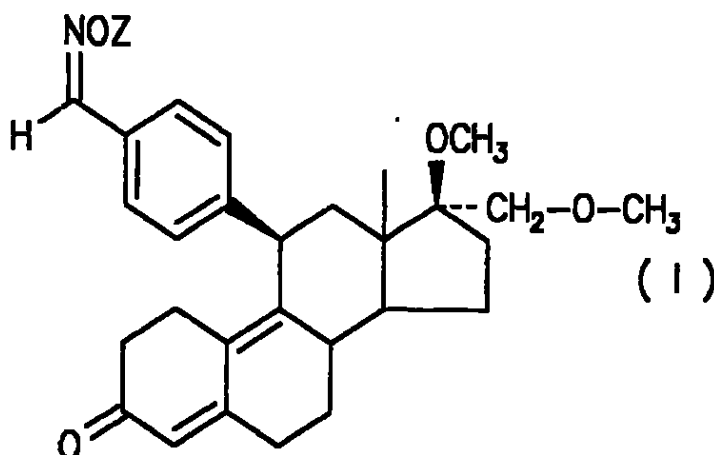
Beispiel 9

Hemmung der frühen Gravidität bei der Ratte

Rattenweibchen werden im Prooestrus angepaart. Bei Nachweis von Spermien im Vaginalabstrich am nächsten Tag wird dieser Tag als Tag 1 (=d1) der Gravidität gerechnet. Die Behandlung mit Testsubstanz oder Vehikel erfolgt von d5-d7, die Autopsie erfolgt d9. Die Substanzen werden in 0,2 ml Vehikel (Benzylbenzoat/Rizinusöl 1 + 4) subcutan injiziert. Die Rate vollständig gehemmter Graviditäten in den verschiedenen Gruppen ergibt sich aus Tabelle 1. Es wurde für J 917 und J 900 eine dem RU 486 überlegene Nidationshemmung festgestellt.

Patentansprüche

- (1) 11 β -Benzaldoxim-estra-4,9-dien-Derivate der allgemeinen Formel I,



worin

Z für -CO-CH₃, -CO-O-C₂H₅, -CO-NH-Phenyl, -CO-NH-C₂H₅, -CO-C₂H₅, -CH₃ oder -CO-Phenyl steht,

sowie deren pharmazeutisch annehmbaren Salze.

- (2) Verbindungen nach Anspruch 1, nämlich

11 β -[4-(Acetoximinomethyl)phenyl]-17 β -methoxy-17 α -methoxymethyl-estra-4,9-dien-3-on,

11 β -[4-(Ethoxycarbonyloximinomethyl)phenyl]-17 β -methoxy-17 α -methoxymethyl-estra-4,9-dien-3-on,

11 β -[4-[(Ethylaminocarbonyl)oximinomethyl]phenyl]-17 β -methoxy-17 α -methoxymethyl-estra-4,9-dien-3-on,

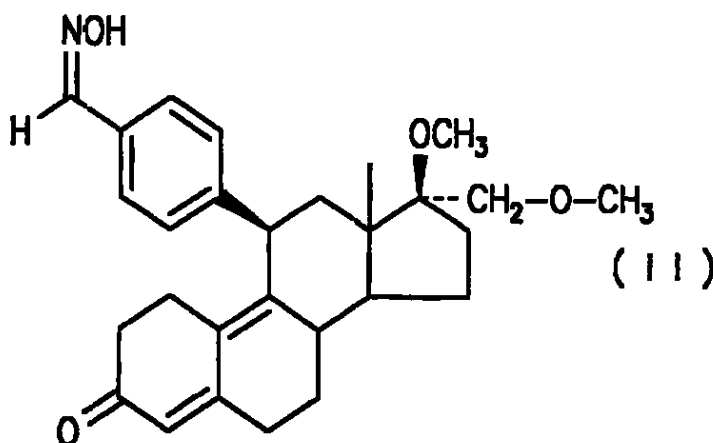
17 β -Methoxy-17 α -methoxymethyl-11 β -[4-[(phenylaminocarbonyl)oximinomethyl]phenyl]-estra-4,9-dien-3-on,

11 β -[4-(Propionyximinomethyl)phenyl]-17 β -methoxy-17 α -methoxymethyl-estra-4,9-dien-3-on,

11 β -[4-(Methyloximinomethyl)phenyl]-17 β -hydroxy-17 α -methoxymethyl-estra-4,9-dien-3-on und

11 β -[4-(Benzoyloximinomethyl)phenyl]-17 β -hydroxy-17 α -methoxymethyl-estra-4,9-dien-3-on.

3. Verfahren zur Herstellung der Verbindungen nach Anspruch 1 und deren pharmazeutisch annehmbaren Salze, dadurch gekennzeichnet, daß man eine Verbindung der allgemeinen Formel II,



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in an sich bekannter Weise verestert oder verethert und gegebenenfalls die erhaltene Verbindung in ein Salz überführt.

④ Pharmazeutische Zusammensetzungen, gekennzeichnet durch den Gehalt an mindestens einer Verbindung nach einem der Ansprüche 1 bis 2.

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DB

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PCT WELTORGANISATION FÜR GEISTIGES EIGENTUM
Internationales Büro
INTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE
INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

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(21) Internationales Aktenzeichen: PCT/EP95/04191 (22) Internationales Anmeldedatum: 24. Oktober 1995 (24.10.95) (30) Prioritätsdaten: P 44 38 820.9 24. Oktober 1994 (24.10.94) DE (71) Anmelder (für alle Bestimmungsstaaten ausser US): SCHERING AKTIENGESELLSCHAFT [DE/DE]; Müllerstrasse 178, D-13342 Berlin (DE). (72) Erfinder; und (75) Erfinder/Anmelder (nur für US): CHWALISZ, Kristof [DE/DE]; Lobber Steig 7a, D-13503 Berlin (DE). STÖCKEMANN, Klaus [DE/DE]; Holsteinische Strasse 33a, D-12161 Berlin (DE). SCHMIDT-GOLLWITZER, Karin [DE/DE]; Palmzelle 10B, D-14129 Berlin (DE). KLEMMANN, Walter [DE/DE]; Kastanienallee 21, D-14052 Berlin (DE).		(81) Bestimmungsstaaten: AU, BG, BR, CA, CN, CZ, EE, FI, HU, JP, KR, LT, LV, MX, NO, NZ, PL, RO, SG, SI, SK, UA, US, europäisches Patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Veröffentlicht Mit internationalem Recherchenbericht. Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist. Veröffentlichung wird wiederholt falls Änderungen eintreffen.
(54) Title: COMPETITIVE PROGESTERONE ANTAGONISTS FOR REGULATING FEMALE FERTILITY AS REQUIRED (54) Bezeichnung: KOMPETITIVE PROGESTERONANTAGONISTEN ZUR BEDARFSORIENTIERTEN WEIBLICHEN FERTILITÄTSKONTROLLE (57) Abstract The present invention concerns the novel use of competitive progesterone antagonists in the preparation of a drug for regulating female fertility as required (pill to be taken as required). This drug can be administered in a single dose at any time during the menstrual cycle, its dosage being less than the ovulation-inhibiting dosage. (57) Zusammenfassung Die vorliegende Erfindung beschreibt die neuartige Verwendung kompetitiver Progesteronantagonisten zur Herstellung eines Arzneimittels zur bedarfsorientierten weiblichen Fertilitätskontrolle (Bedarfpille), welches unabhängig vom Zeitpunkt des Menstruationszyklus angewandt werden kann, in einer einmalig zu verabreichenden Dosisform, deren Dosierung unterhalb der ovulationsinhibierenden Dosierung liegt.		

Kompetitive Progesteronantagonisten zur bedarfsorientierten weiblichen Fertilitätskontrolle

Die vorliegende Erfindung betrifft die Verwendung mindestens eines kompetitiven Progesteronantagonisten zur Herstellung eines Arzneimittels zur bedarfsorientierten weiblichen Fertilitätskontrolle ("Bedarfs-Pille"), welches unabhängig vom Zeitpunkt des Menstruationszyklus angewandt werden kann, in einer einmalig zu verabreichenden Doseinheit, deren Dosierung unterhalb der ovulationsinhibierenden Dosierung liegt.

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Bereits auf der ganzen Welt hat sich der Gebrauch von oralen Kontrazeptiva zu einem gesellschaftlichen Faktor entwickelt, der nicht mehr wegzudenken ist. Besonders unter dem Aspekt der sich nach wie vor rasant entwickelnden Weltbevölkerung ist eine Weiterentwicklung der bislang bewährten Methoden zur Fertilitätskontrolle unbedingt erforderlich.

Der Einsatz von kompetitiven Progesteronantagonisten in der weiblichen Fertilitätskontrolle wird sowohl bei diversen Tierspezies als auch am Menschen schon seit einigen Jahren diskutiert, wie den nachfolgend aufgeführten Publikationen entnommen werden kann, wobei insbesondere der Einsatz von RU 486 (11-β-[4-N,N-(dimethylamino)phenyl]-17-β-hydroxy-17-α-propinyl-estra-4,9(10)-dien-3-on; EP-A-0057115) in diesem Zusammenhang aufgeführt wurde:

Collins et al., Blockade of the spontaneous mid-cycle gonadotropin surge in monkeys by RU 486; A progesterone antagonist or agonist. J. Clin. Metab., 63:1270-1276 (1986);

Croxatto, H.B., Salvatierra 1990 Cyclic use of antigestagens for fertility control. IIIrd International Symposium on Contraception, Heidelberg, June 19-23, 1990;

Danford et al., Contraceptive potential of RU 486 by ovulation inhibition. III. Preliminary observations on once weekly administration. Contraception 40: 195-200 (1989);

Kekkonen et al., Lihteenmäki P 1990 Interference with ovulation by sequential treatment with the antiprogesterone RU 486 and synthetic progestin. Fertil Steril [Fertile Sterile] 53: 4747 (1990);

Puri et al., Gonadal and pituitary responses to progesterone antagonist ZK 98 299 during the follicular phase of the menstrual cycle in bonnet monkeys. Contraception 39(2): 227-243 (1989);

5.

Gerade für Frauen, die sich nicht zu der bislang erforderlichen, regelmäßigen Einnahme von oralen Kontrazeptiva entschließen konnten oder auch aus anderen, z.B. medizinischen Gründen nicht die Möglichkeit hatten, diese Form der Fertilitätskontrolle zu wählen, bietet sich nunmehr die Alternative, sich für die einmalige, bedarfsorientierte Einnahme eines oralen Kontrazeptivum zu entscheiden, ohne ihren Organismus einer den gesamten Menstruationszyklus fortdauernden hormonellen Kontrolle auszusetzen.

Die vorliegende Erfindung besitzt des weiteren wesentliche Vorteile, die nicht zuletzt in der niedrigen Dosierung des Wirkstoffes begründet liegen.

So wird der weibliche Menstruationszyklus in keiner Weise in seiner Zyklizität beeinträchtigt (wie durch ovulationshemmende Substanzen verursacht) und der Organismus nicht durch unnötig hohe Mengen des kompetitiven Progesteronantagonisten belastet.

Der Gebrauch eines solchen Progesteronantagonisten bietet ferner eine sichere Empfängnisverhütung, d.h. die einmalige Einnahme eines derartigen Medikamentes verhindert die Einnistung der Blastozyste.

Die kompetitiven Progesteronantagonisten werden gemäß vorliegender Erfindung in Mengen von im allgemeinen einmalig 1 - 400 mg Onapriston oder einer biologischen Äquivalentdosis eines anderen kompetitiven Progesteronantagonisten verwendet.

Die Behandlung mit dem kompetitiven Progesteronantagonisten wird in der Regel durch die einmalige, bedarfsorientierte, d.h. im allgemeinen prä- oder auch postkoitale Einnahme einer Tagesdosisseinheit unabhängig vom Zykluszeitpunkt vorgenommen.

Die präkoitale Einnahme des erfindungsgemäß hergestellten Medikaments ist bevorzugt. Der Zeitpunkt der Einnahme kann bis zu 6 Stunden vor oder bis zu 24 Stunden nach dem Koitus liegen.

Die Einnahme ist dabei zu jedem Zykluszeitpunkt, an dem eine kontrazeptive Maßnahme erforderlich, angeraten oder gewünscht ist, möglich.

Als kompetitive Progesteronantagonisten sind erfindungsgemäß alle Verbindungen geeignet, die eine entsprechend charakteristische Affinität zum Progesteronrezeptor zeigen und eine Endometrium-selektive Wirkung aufweisen. Derartige Progesteronantagonisten zeigen in der eingesetzten Dosierung eine Nidationshemmung ohne eine Hemmung der Ovulation zu bewirken. So kommen beispielsweise die folgenden Progesteronantagonisten infrage:

11 β -[4-N,N-(Dimethylamino)phenyl]-17 α -hydroxy-17 β -(3-hydroxypropyl)-13 α -methyl-4,9(10)-gonadien-3-on (EP-A 0 129 499),
 11 β -(4-Acetylphenyl)-17 β -hydroxy-17 α -(3-hydroxyprop-1(Z)-enyl)-4,9(10)-estradien-3-on (EP-A 0 190 759),
 11 β ,19-[4-(Cyanphenyl)-o-phenylen]-17 β -hydroxy-17 α -(3-hydroxyprop-1(Z)-enyl)-4-androsten 3-on,
 11 β ,19-[4-(3-Pyridinyl)-o-phenylen]-17 β -hydroxy-17 α -(3-hydroxyprop-1(Z)-enyl)-4-androsten 3-on (beide WO-A 93/23020)
 17 α -Hydroxy-17 β -(3-hydroxypropyl)-11 β -[4-(1-methylethenyl)phenyl]-13 α -estra-4,9-dien-3-on,
 11 β -[4-(3-Furanyl)phenyl]-17 α -hydroxy-17 β -(3-hydroxypropyl)-13 α -estra-4,9-dien-3-on (beide EP-A 0 349 481),
 (Z)-11 β -[4-(Dimethylamino)phenyl]-17 β -hydroxy-17 α -(3-hydroxyprop-1-enyl)estr-4-en-3-on (EP-A 0 404 283),
 11 β -[4-[[[(Acetyloxy)imino]methyl]phenyl]-17 β -methoxy-17 α -(methoxymethyl)estra-4,9-dien-3-on (EP-A 0 648 778, EP-A 0 648 779),
 11 β -[4-[[[(Ethoxycarbonyl)oxy]imino]methyl]phenyl]-17 β -methoxy-17 α -(methoxymethyl)estra-4,9-dien-3-on (EP-A 0 648 778, EP-A 0 648 779).
 11 β -[4-(Acetyl)phenyl]-19,24-dinor-17,23-epoxy-17 α -chola-4,9,20-trien-3-on,
 (11 β ,17 α)-11-[4-(Acetyl)phenyl]-17,23-epoxy-19,24-dinorchola-4,9,20-trien-3-on.

Die kompetitiven Progesteronantagonisten können beispielsweise lokal, topisch, enteral oder parenteral appliziert werden.

Für die bevorzugte orale Applikation kommen insbesondere Tabletten, Dragées, Kapseln, Pillen, Suspensionen oder Lösungen infrage, die in üblicher Weise mit den in der Galenik gebräuchlichen Zusätzen und Trägersubstanzen hergestellt werden können.

Die einmalig zu verabreichende orale Dosierungseinheit enthält etwa 2 bis 200 mg Onapriston oder die biologische Äquivalentdosis (wirkequivalente Menge) eines anderen dissoziierten kompetitiven Progesteronantagonisten.

Als wirkequivalente Menge gilt die Dosis, die beim Cynomolgus-Affen nach einer einmaligen Behandlung am Tag 22 des Zyklus die vorzeitige Menstruation induziert, die Ovulation, wenn vor dem LH-Peak (LH - 2) einmalig verabreicht, aber nicht hemmt.

Patentansprüche

① Verwendung mindestens eines kompetitiven Progesteronantagonisten zur Herstellung eines Arzneimittels zur bedarfsorientierten weiblichen Fertilitätskontrolle, welches unabhängig vom Zeitpunkt des Menstruationszyklus angewandt werden kann, in einer einmalig zu verabreichenden Dosis Einheit, deren Dosierung unterhalb der ovulationsinhibierenden Dosierung liegt.

② Verwendung nach Anspruch 1, dadurch gekennzeichnet, daß der kompetitive Progesteronantagonist aus der Gruppe der folgenden Verbindungen ausgewählt ist:

- 11 β -[4-N,N-(Dimethylamino)phenyl]-17 α -hydroxy-17 β -(3-hydroxypropyl)-13 α -methyl-4,9(10)-gonadien-3-on,
- 11 β -(4-Acetylphenyl)-17 β -hydroxy-17 α -(3-hydroxyprop-1(Z)-enyl)-4,9(10)-estradien-3-on,
- 11 β ,19-[4-(Cyanphenyl)-o-phenylen]-17 β -hydroxy-17 α -(3-hydroxyprop-1(Z)-enyl)-4-androsten 3-on,
- 11 β ,19-[4-(3-Pyridinyl)-o-phenylen]-17 β -hydroxy-17 α -(3-hydroxyprop-1(Z)-enyl)-4-androsten 3-on,
- 17 α -Hydroxy-17 β -(3-hydroxypropyl)-11 β -[4-(1-methylethenyl)phenyl]-13 α -estra-4,9-dien-3-on,
- 11 β -[4-(3-Furanyl)phenyl]-17 α -hydroxy-17 β -(3-hydroxypropyl)-13 α -estra-4,9-dien-3-on,
- (Z)-11 β -[4-(Dimethylamino)phenyl]-17 β -hydroxy-17 α -(3-hydroxyprop-1-enyl)estr-4-en-3-on (EP-A 0 404 283),
- 11 β -[4-[[[(Acetyloxy)imino]methyl]phenyl]-17 β -methoxy-17 α -(methoxymethyl)estra-4,9-dien-3-on (EP-A 0 648 778, EP-A 0 648 779),
- 11 β -[4-[[[(Ethoxycarbonyl)oxy]imino]methyl]phenyl]-17 β -methoxy-17 α -(methoxymethyl)estra-4,9-dien-3-on (EP-A 0 648 778, EP-A 0 648 779),
- 11 β -[4-(Acetyl)phenyl]-19,24-dinor-17,23-epoxy-17 α -chola-4,9,20-trien-3-on,
- (11 β ,17 α)-11-[4-(Acetyl)phenyl]-17,23-epoxy-19,24-dinorchola-4,9,20-trien-3-on.

3. Verwendung nach Anspruch 1, dadurch gekennzeichnet, daß der kompetitive Progesteronantagonist aus der Gruppe der folgenden Verbindungen ausgewählt ist:

17 β -(3-Acetoxypropyl)-11 β -[4-N,N-(dimethylamino)phenyl]-17 α -hydroxy-13 α -methyl-4,9(10)-gonadien-3-on,

17 β -(3-Benzoyloxypropyl)-11 β -[4-N,N-(dimethylamino)phenyl]-17 α -hydroxy-13 α -methyl-4,9(10)-gonadien-3-on.

4. Verwendung nach Anspruch 1, dadurch gekennzeichnet, daß der kompetitive Progesteronantagonist in dem Arzneimittel zur Applikation in lokaler, topischer, enteraler oder parenteraler Weise bergerichtet ist.

5. Verwendung nach Anspruch 1, dadurch gekennzeichnet, daß der kompetitive Progesteronantagonist in der einmalig zu verabreichenden Dosiseinheit in einer Menge von 1 bis 400 mg enthalten ist bzw. aus dieser in einer Menge von 1 bis 400 mg freigesetzt wird.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/EP97/02371 (22) International Filing Date: 7 May 1997 (07.05.97) (30) Priority Data: 08/646,518 7 May 1996 (07.05.96) US (71) Applicant: SCHERING AKTIENGESELLSCHAFT [DE/DE]; Müllerstrasse 178, D-13353 Berlin (DE). (72) Inventors: CHWALSZ, Krzysztof; Lobber Steig 7a, D-13503 Berlin (DE). GARFIELD, Robert, E.; 1814 Winding Way, Friendswood, TX 77546 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: IMPROVEMENT OF IMPLANTATION RATES AFTER IN VITRO FERTILIZATION		
(57) Abstract A method is provided for the improvement of implantation rates and/or pregnancy rates in a female mammal, comprising administering to a female mammal in whom pregnancy is desired an effective amount of: (a) a nitric oxide synthase substrate, a nitric oxide donor, or both, optionally in combination with, (b) a progestin, and, (c) optionally, in further combination with an estrogen. A method is also provided for fertility control for a female mammal, comprising administering to a female mammal in whom pregnancy is not desired and at risk of becoming pregnant an effective amount of nitric oxide synthase inhibitor in combination with an antiprogestin. Pharmaceutical compositions are also provided.		

IMPROVEMENT OF IMPLANTATION RATES AFTER IN VITRO FERTILIZATION

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Background of the invention

This invention relates to a method for the improvement of implantation rates after in vitro fertilization (IVF), for the treatment of infertility and for the treatment and prevention of early pregnancy loss in women with a nitric oxide synthase substrate (L-arginine), a nitric oxide donor or both, alone or in combination with progesterone and/or estrogen. This invention also relates to the novel methods of fertility control based on inhibition of endometrial receptivity, prevention of implantation, and menstrual induction with NOS inhibitors, preferentially INOS inhibitors, in combination with progesterone antagonists, and/or progesterone synthase inhibitors.

Human in vitro fertilization is surprisingly unsuccessful. The overall birth rate per IVF treatment cycle is approximately 14% in USA (*Medical Research International Society for Assisted Reproductive Technology [SART], The American Fertility Society [1992]. Fertil Steril 5:15*), and 12.5% in UK (*The Human Fertilization and Embryology Authority. Annual Report, London 1992*).

Success is greater when more than one embryo is transferred simultaneously. However, simultaneous transfer of multiple embryos increases the incidence of multiple pregnancy and the possibility of miscarriage and prematurity. The reasons for the low pregnancy rates after IVF are still not completely understood. The quality of both the embryo and the uterine environment affects success. Generally, there is a high rate of spontaneous early abortion in fertile cycles in women. After natural conception, possibly as many as 50-60% of very early pregnancies are lost (*Winston ML, Handyside AH [1993], New challenges in human in vitro fertilization. Science 260:932-935*). This may be due to both conceptus abnormalities and dysynchrony between embryo and endometrium at the time of embryo transfer.

Most losses may be due to abnormalities of the conceptus or the still inappropriate culture conditions, since the success of embryo transfer after IVF decreases as the time after

It is another object of the invention to provide a method for treatment and prevention of infertility or early pregnancy loss comprising administering a nitric oxide substrate and/or donor in early pregnant mammals.

5 It is a further object of the invention to provide a method for improvement of implantation and treatment and prevention of infertility or early pregnancy loss comprising administering a nitric oxide substrate and/or donor in which progesterone or a progestagenic agent in combination with a nitric oxide substrate and/or donor is used.

10 It is another object of this invention to provide a method in which a progestational agent and an estrogenic agent are administered in combination with a nitric oxide substrate and/or nitric oxide donor for the for improvement of implantation and treatment and prevention of infertility or early pregnancy loss female mammals.

15 It is another object of this invention to provide a method for fertility control comprising administering antiprogesterin (e.g. mifepristone, ORG 31710, ORG 33 628, J867, CDB 2914, ZK 137316) and/or progesterone synthase inhibitor (e.g. epostane, trilostane) in combination with an nitric oxide synthase inhibitor.

20 It is another object of this invention to provide a method for fertility control comprising administering an antiprogesterin and/or a progesterone synthase inhibitor in combination with an nitric oxide synthase inhibitor for once-a-month contraception.

25 It is another object of this invention to provide a method for fertility control comprising administering an antiprogesterin in combination with an nitric oxide synthase inhibitor for termination of early pregnancy.

30 A further object is the provision of pharmaceutical compositions useful in practicing the methods of this invention. Upon further study of the specification and appended claims, further objects and advantages of this invention will become apparent to those skilled in the art.

Summary of the Invention

In a method aspect, this invention relates to a method of improving implantation rates after IVF or treating of early pregnancy loss which comprises administering to an individual manifesting the symptoms thereof one or both of a nitric oxide substrate and a nitric oxide donor, alone or in combination with progesterone alone or in further combination of an estrogen in amounts effective to ameliorate the symptoms thereof, the amount of the nitric oxide synthase substrate and nitric oxide donor or both being effective to increase implantation and birth rates by raising the blood level of circulating L-arginine in a female to whom the composition is administered to at least 10 to 500 μ mole above the normally 50-1000 μ mole circulating levels or raise nitric oxide donor levels to about 10 nM to 100 μ M (micromolar), the amount of the progestational agent administered being bioequivalent to 10-300 mg of injected progesterone, and the amount of the estrogen being bioequivalent to approximately 2 mg per day of estradiol (Progynova^R, Schering).

In a method aspect, this invention relates to a method of fertility control which comprises administering to a female mammal a nitric oxide inhibitor and an antiprogesterin, alone or in combination with a progesterone synthase inhibitor. In one embodiment, this fertility control is effected prior to implantation. A nitric oxide inhibitor, preferentially an iNOS inhibitor, can be used in combination with an antiprogesterin for the inhibition of implantation after administration during the periovulatory period (LH peak $\pm$ 4 days), as emergency contraception (i.e. within 72 hours of an unprotected intercourse), for the inhibition of endometrial receptivity using continuous daily treatment, for the inhibition of endometrial receptivity using once-a-week treatment, for menstrual induction (i.e. within the first week of amenorrhoea of the fertile cycle), or regularly for menstrual induction every 28 $\pm$ 3 days.

In a product aspect, this invention relates to a pharmaceutical composition comprising at least one of a nitric oxide synthase substrate (L-arginine) and a nitric oxide donor (e.g. sodium nitroprusside or glyceryl trinitrate), alone or in further combination with one or more of a progesterone/progestin and/or estradiol/estrogen with the amount of the nitric oxide synthase substrate, a nitric oxide donor or both per unit dosage being equivalent to either raise the blood level of circulating L-arginine to least 10 to 500 μ M above the normally 50 to 1000 μ M circulating or raise nitric oxide donor levels to about 10 nM to 100 μ M, the amount of the estrogen being bioequivalent to about 2 mg of estradiol (e.g. Progynova^R, Schering) with the amount of the progesterone bioequivalent to 5 to 300 mg of injected progesterone.

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In a product aspect, this invention relates to a pharmaceutical composition comprising at least one of a nitric oxide synthase inhibitor, preferentially an iNOS inhibitor (e.g. L-NMMA, L-NIO, L-NIL, aminoguanidine, AMT, 4-methyl-2-aminopyridine, 6,4-dimethyl-2-aminopyridine, or 2-aminopyridine) in an effective dose in combination with an antiprogestin alone or/and in further combination with a progesterone synthase inhibitor.

Detailed Disclosure

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The methods of this invention improve the implantation and birth rates after IVF and treat early pregnancy loss in pregnant female, who is manifesting the symptoms thereof.

15 Because the low implantation and birth rates and early pregnancy loss are produced by or aggravated by inadequate uterine blood supply to the conceptus due to insufficient or subnormal nitric oxide synthesis, both nitric oxide synthase substrates, e.g., L-arginine and nitric oxide donors, e.g., sodium nitroprusside, nitroglycerin, glyceryl trinitrate, SIN-1, isosorbid mononitrate isosorbid dinitrate and diethylenetriamine/NO (DETA/NO), are useful for ameliorating the symptoms thereof and, in one respect of this method of this invention, a combination of both are employed.

20 An additive effect is achieved when a progestagenic and/or and estrogenic agent is administered concurrently with a nitric oxide substrate and/or nitric oxide donor. In the case of a female mammal, a progestagenic agent can be administered concurrently with or in lieu of an estrogen.

25 Thus, the method aspect of this invention and the pharmaceutical composition aspect of this invention employs either or both of a nitric oxide substrate and a nitric oxide donor and, optionally one or more of an estrogen (e.g., Progynova^R, Schering) or a progestin (e.g. progesterone or hydroxyprogesterone caproate [Proluton^R Depot], etc.).

30 In the method aspect of this invention regarding the fertility control, a synergistic or additive effect is achieved when a progesterone receptor antagonist (antiprogestin) and/or a progesterone synthase inhibitor is administered concurrently with a nitric oxide synthase inhibitor, preferentially an iNOS inhibitor.

The pharmaceutical preparations can be sterilized and if desired mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, flavoring and/or aromatic substances and the like which do not deleteriously react with the active compounds.

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For parental application, particularly suitable are solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions, or implants, including suppositories, transdermal patches, and vaginal gels, creams and foams. Ampoules are convenient unit dosages.

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In a preferred aspect, the composition of this invention is adapted for ingestion.

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For enteral application, particularly suitable are unit dosage forms, e.g., tablets, dragees or capsules having talc and/or carbohydrate carrier or binder or the like, the carrier preferably being lactose and/or corn starch and/or potato starch; particulate solids, e.g., granules; and liquids and semi-liquids, e.g., syrups and elixirs or the like, wherein a sweetened vehicle is employed. Sustained release compositions can be formulated including those wherein the active compound is protected with differentially degradable coatings, e.g., by microencapsulation, multiple coatings, etc.

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Suitable for oral administration are, inter alia, tablets, dragees, capsules, pills, granules, suspensions and solutions. Each unit dose, e.g., each table spoon of liquid or each tablet, or dragee contains, for example, 5 - 5000 mg of each active agent.

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Suitable for transdermal application are inter alia transdermal patches and gels.

Solutions for parenteral administration contain, for example, 0.01 - 1% of each active agent in an aqueous or alcoholic solution.

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The nitric oxide substrate and/or donor can be administered as an admixture with an estrogen and/or progestational agent and any other optional active agent or as a separate unit dosage form, either simultaneously therewith or at different times during the day from each other.

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The combination of active agents is preferably administered at least once daily (unless administered in a dosage form which delivers the active agents continuously) and more

preferably several times daily, e.g., in 2 to 6 divided doses. The typical dose is about 0.5 to 1000 mg of each active agent, although some less active agents, e.g., L-arginine, require much higher oral dosages, e.g., 500 to 10,000 mg, and others, e.g., sodium nitroprusside, require lower doses, e.g., 500 -2,000 µg/kg/day. Doses for nitroglycerine typically are orally
5 2.6 mg 2 x daily; sublingually, 0.8 mg 1-4 x daily; and transdermally, 0.2 - 0.5 mg/hr. The preferred administration form is a transdermal application. Since the LD50 dosages of most of these active agents is known in the prior art, a lower dosage regimen can be initiated and the dosage increased until a positive effect is achieved or a higher dosage regimen can initially be employed, e.g., in a crisis situation, and the dosages regulated downward as
10 relief from the symptoms is achieved. Combinations of agents can be employed either continuously or sequentially.

In humans, both L-arginine and progesterone (or bioequivalent of another progestin) should be given in a ratio which produces blood plasma levels of 50 - 5000 µmolar L-
15 arginine, 10 - 100 nmolar estradiol and 100 to 1000 nmolar of progesterone .

The nitric oxide synthase inhibitor, preferentially INOS inhibitor, can be administered as an admixture with an antiprogestin and/or progesterone synthase inhibitor (e.g.
20 epostane, trilostane) and any other optional active agent or as a separate unit dosage form, either simultaneously therewith or at different times during the day from each other.

Brief Description of the Drawings

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Various other objects, features and attendant advantages of the present invention will be more fully appreciated as the same becomes better understood when considered in conjunction with the accompanying drawings, in which like reference characters designate the same or similar parts throughout the several views, and wherein:

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Figure 1: Figure 1 shows the effects of L-NAME (NOS inhibitor) on implantation in rats. The animals were treated with 25 and 50 mg/animal/day L-NAME administered via continuous s.c. infusion from day 1 post coitum (p.c.) until
35 day 7 p.c. The autopsy was performed on day 12 p.c.

250-1000 mg/week I.m.) and estradiol valerate 0.5 - 4 mg/day for the first 2-6 weeks of pregnancy or longer.

- 5 **Example 8:** Postcoital contraception with a nitric oxide synthase inhibitor in combination with an antiprogestin. Administer 0.5-400 mg antiprogestin/day (e.g. mifepristone) in combination with a nitric oxide synthase inhibitor, preferentially INOS inhibitor, at an effective dose within 72 hours after the intercourse
- 10 **Example 9:** Endometrial contraception with a nitric oxide synthase inhibitor in combination with an antiprogestin using daily administration. Administer an antiprogestin at a daily dose which does not inhibit ovulation (e.g. 0.1 -1 mg/day mifepristone) in combination with a nitric oxide synthase inhibitor, preferentially INOS inhibitor at an effective dose.
- 15 **Example 10:** Endometrial contraception with a nitric oxide synthase inhibitor in combination with an antiprogestin using once-a-week administration. Administer once-a-week an antiprogestin at a dose which does not inhibit ovulation (e.g. 5-20 mg/week mifepristone) in combination with a nitric oxide synthase inhibitor, preferentially INOS inhibitor at an effective dose.
- 20 **Example 11:** Menstrual induction with a nitric oxide synthase inhibitor in combination with an antiprogestin. Administer 0.5-400 mg/day antiprogestin (e.g. mifepristone) in combination with a nitric oxide synthase inhibitor, preferentially INOS inhibitor, at an effective dose on day 28 +/-3 days of the menstrual cycle.
- 25 **Example 12:** Menstrual induction with a nitric oxide synthase inhibitor in combination with a progesterone synthase inhibitor. Administer 1-800 mg/day progesterone synthase inhibitor (e.g. epostane) in combination with an nitric oxide synthase inhibitor, preferentially INOS inhibitor, at an effective dose on day 28 +/-3 days of the menstrual cycle.
- 30 **Example 13:** Menstrual induction with a nitric oxide synthase inhibitor in combination with an antiprogestin and in a further combination with a progesterone synthase
- 35

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10. The method of claim 8, wherein the progestin is progesterone or hydroxyprogesterone caproate
- 5 11. The method of claim 9, wherein the estrogen is estradiol valerate
12. The method of fertility control with a nitric oxide synthase inhibitor in combination with an antiprogesterin
- 10 13. The method of claim 12, wherein the antiprogesterin is mifepristone, ORG 31710, ORG 33 628, J667, CDB 2914, or ZK 137316
14. The method of claim 12, wherein the treatment is performed postcoitally
- 15 15. A pharmaceutical composition comprising an admixture of (a) a nitric oxide synthesis substrate, (b) a nitric oxide donor or both, and optionally, also at least one of (c) a progestin, (d) and an estrogen in amounts effective to increase the pregnancy rates or ameliorate the symptoms of threatening abortion in a pregnant or infertile female mammal when administered thereto in an amount effective of estrogen equivalent to 1 - 2 mg of estradiol and an amount of the progestin bioequivalent to 50 - 300 mg of injected progesterone and an amount of the nitric oxide synthase substrate, nitric oxide donor or both effective to raise the blood level of circulating L-arginine to at least about 50 - 5000 μ molar above the normally 50 - 1000 μ molar circulating levels or raise the nitric oxide donor levels to about 10nM to 100 μ molar.
- 20 16. The composition according to claim 15, wherein (a) is a nitric oxide synthesis substrate.
- 30 17. The composition according to claim 16, wherein the nitric oxide synthesis substrate (b) is L-arginine.
- 35 18. The composition according to claim 14, wherein (b) is a nitric oxide donor.

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- 5
27. A method of claim 25, wherein the nitric oxide synthase substrate is L-arginine.
28. A method of claim 25, wherein the mammal is a pregnant human female and a nitric oxide donor is administered thereto.
- 10
29. A method of claim 28, wherein the nitric oxide donor is sodium nitroprusside, nitroglycerin, glyceryltrinitrate, SIN-1, isosorbid mononitrate or isosorbid dinitrate.
30. A method of claim 28, wherein the nitric oxide donor is administered orally.
31. A method of claim 28, wherein the nitric oxide donor is administered transdermally.
- 15
32. A method of claim 25, wherein the mammal is a pregnant human female and a nitric oxide substrate or donor is administered thereto in combination with a progestin.
- 20
33. A method of claim 25, wherein the mammal is a pregnant human female and a nitric oxide substrate or donor is administered thereto in combination with a progestin and an estrogen.
- 25
34. A method of claim 32, wherein the progestin is progesterone or hydroxyprogesterone caproate.
35. A method of claim 33, wherein the estrogen is estradiol valerate.
- 30
36. A method of fertility control for a female mammal, comprising administering to a female mammal in whom pregnancy is not desired and a risk for becoming pregnant an effective amount of nitric oxide synthase inhibitor in combination with an antiprogestin.
- 35
37. A method of claim 36, wherein the antiprogestin is mifepristone, ORG 31 10, ORG 33 628, J867, CDB 2914, or ZK 137316.

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38. A method of claim 36, wherein the method is performed postcoitally.
39. A method of claim 25, wherein the mammal is a human female and the amount of the nitric oxide synthase substrate, nitric oxide donor or both administered is effective to raise the blood level of circulating L-arginine in said female to at least about 50 - 5000 μ mole circulating levels.
40. A method of claim 25, wherein the mammal is a human female and the amount of the nitric oxide synthase substrate, nitric oxide donor or both administered is effective to raise the nitric oxide donor level to about 1 - 1000 nmolar.
41. A method of claim 25, wherein the mammal is a human female and the amount of progestin administered is bioequivalent to 50 - 300 mg of injected progesterone, and the amount of estrogen administered, if any, is bioequivalent to 1 - 2 mg of estradiol.
42. A pharmaceutical composition comprising an admixture of effective amounts of
- a) a nitric oxide synthesis substrate, a nitric oxide donor or both; and
 - b) a progestin, and optionally,
 - c) an estrogen,
- In amounts effective to increase the pregnancy rates or ameliorate the symptoms of impending abortion in pregnant female mammal or a female mammal with impaired fertility, wherein the amount of nitric oxide synthase substrate, nitric oxide donor or both administered is effective to raise the blood level of circulating L-arginine in said female to whom the composition is administered to at least about 50 - 5000 μ molar above the normally 50 - 1000 μ mole circulating levels and/or is effective to raise the nitric oxide donor level to about 1 - 1000 nmolar; the amount of progestin administered is bioequivalent to 50 - 300 mg of injected progesterone; and the amount of estrogen administered, if any, is bioequivalent to 1 - 2 mg of estradiol.
43. A composition of claim 42, wherein (a) is a nitric oxide synthase substrate.

44. A composition of claim 43, wherein the nitric oxide synthesis substrate is L-arginine.
- 5 45. A composition of claim 42, wherein (a) is a nitric oxide donor.
46. A composition of claim 45, wherein the nitric oxide donor is sodium nitroprusside, nitroglycerin, glyceryltrinitride, SIN-1, isosorbid mononitrate or isosorbid dinitrate.
- 10 47. A composition of claim 42, wherein (b) is progesterone or hydroxyprogesterone caproate.
48. A composition of claim 42, wherein (c) is estradiol valerate.
- 15 49. A method of claim 25, wherein components (a) and (b) are administered sequentially.
- 20 50. A method of claim 25, wherein components (a) and (b) are administered simultaneously.

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(54) Title: PROGESTOGEN-ANTI-PROGESTOGEN REGIMENS (57) Abstract Disclosed is a contraceptive and/or HRT (hormone replacement therapy) kit comprising sequential daily dosage units each containing as the sole contraceptively effective ingredient of a progestogen, or as effective ingredient for HRT a progestogen with or without an estrogen or an estrogen only, and further two or more dosage units comprising an anti-progestogen. One of the anti-progestogen is administered at the beginning and the others regularly divided throughout the cycle, preferably one only in the middle of the cycle.		

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While different progestogen-only regimens have been described, they are still associated with incomplete ovulation inhibition, and relatively high failure rates. Veasey et al "Progestogen-only oral contraception. Findings in a large prospective study with special reference to effectiveness", Brit. J. Family Planning, 292: 526-30 (1986). It has been suggested to increase the daily dosage of progestogen in order to induce complete ovulation inhibition, however such an increase in dosage also increases the frequency of intermenstrual bleeding (i.e. "spotting"), which is clearly not desired. E. Diczfalussy et al, Progestogens in Therapy, p. 150 (Raven Press, NY 1983). Moreover, a high prevalence of functional ovarian cysts have been reported with progestogen only contraceptive regimens, which resolve after discontinuation of the progestogen-only contraceptive. Fotherby, K. "The Progestogen-pill", in: Filshie et al eds. Contraception: Science and Practice, pp. 94-108 (1989), and Howie, supra. A need exists for a progestogen-only contraceptive regimen which more effectively inhibits ovulation, while still not increasing the frequency of intermenstrual bleeding, or leading to persistent functional ovarian cysts. The solution to this need by adding intermittently an anti-progestogen needs further elaboration.

Surprisingly it has now been found that apart from administering an anti-progestagen at the beginning of a cycle, by selecting one or more additional days during the cycle, preferably one day in the middle of the cycle, on which the anti-progestogen is administered, whereas over the rest of an entire menstrual cycle (e.g. 28 days) desogestrel or 3-ketodesogestrel is administered as the progestogen at certain specified dosages, complete ovulation inhibition is achieved, while retaining good cycle control and almost completely decreasing the amount of spotting.

The invention thus includes a drug delivery system for contraceptive use containing daily oral dosage units, each unit containing a progestogen, and two or more units comprising an anti-progestogen, one of which is administered at the end and the others orderly divided through the cycle (if one: in the middle of the cycle).

The invention also includes a drug delivery system for HRT (hormone replacement therapy) containing daily oral dosage units, each unit comprising a progestogen with or without an estrogen or an estrogen only, and two or more dosage units comprising an anti-progestogen, one of which is preferably administered at the beginning and the others orderly divided through the cycle (if one: in the middle of the cycle).

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In general terms the invention relates to a contraceptive and/or HRT (hormone replacement therapy) kit comprising sequential daily dosage units for oral administration each comprising as the sole contraceptively effective ingredient a progestogen, or as effective ingredient for HRT a progestogen with or without an estrogen or an estrogen alone, and further two or more units comprising an anti-progestogen.

If desired the kits may contain placebo pills to bridge two periods of administration of active ingredients. This is usual for contraceptive regimens containing less than 28 dosage units, in order to obtain a kit still having 28 pills (the usual cycle).

The invention also includes a pharmaceutical product (i.e. the dosage units or the package containing the dosage units), a method of using the product, and a process of manufacturing the pharmaceutical product.

The invention also includes a method of providing contraception and/or HRT for a pre-, peri-, or post-menopausal woman involving administering to the woman the above-mentioned regimens.

Progestogens for use with the invention are 3-keto-desogestrel (etonogestrel), desogestrel, gestodene, levonorgestrel, norgestrel and other progestogens commonly used for contraception and HRT. Desogestrel has the chemical name 13-ethyl-11-methylene-18,19-di-nor-17 α -pregn-4-en-20-yn-17-ol, and is the preferred progestogen. Desogestrel is believed to be metabolized in the body into 3-ketodesogestrel. Preferred the dosage units contain 75 μ g of desogestrel or 3-ketodesogestrel, or amount of other progestogens having the equivalent effect as 75 μ g of desogestrel. Based on practically applied doses, levonorgestrel, desogestrel, and 3-keto-desogestrel are relatively equipotent in progestogenic activity. Gestodene is approximately 1.5 times as potent as these compounds. Norgestrel is about one-half as potent as levonorgestrel.

The anti-progestogen can be an inhibitor of progesterone synthesis, such as epostane, azastene or trilostane (Creange, Contraception 24, 289, 1981; Drugs of the Future 7,

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661, 1982, van der Spuy et al., Contraception 35, 111, 1987; US patent 3296255) or a progesterone receptor antagonist, or any such pharmaceutically suitable agent that counteracts the normal biological activity of progesterone, such as antibodies or ligands bindable to progestogens or to the progesterone receptor.

5 A suitable anti-progestogen is a progesterone receptor antagonist. For example RU486, Onapristone, Org 31710 [(6 α ,11 β ,17 β)-11-(4-dimethylaminophenyl)-6-methyl-4',5'-dihydrospiro[estra-4,9-diene-17,2'-(3'H)-furan]-3-one], and Org 33628 [11 β ,17 α)-11-(4-acetylphenyl)-17,23-epoxy-19,24-dinorchols-4,9,20-trien-3-one] are particularly suitable in the practice of the present invention.

10 Suitable amounts of anti-progestogen are for example 0.1 to 300 mg, and preferably 0.5 to 150 mg of Org 31710 or such amounts of other anti-progestogens which have equivalent activity. The anti-progestogen is administered at the beginning of the cycle, preferably on day 1, and in the middle of the cycle, preferably day 14. More generally, the first of the anti-progestogen dosage units may be administered between days 1 and
15 3 (the beginning of the cycle), and the second between days 12 and 16 (the middle of the cycle). In the case of more than one additional day of anti-progestagen administration, these additional days may be, e.g., in the middle of the remaining phases, i.e. anti-progestagen then is administered once a week. Maximally, the anti-progestagen can be administered every 4 days, i.e. for a cycle of 28 days the number
20 of dosage units comprising anti-progestagen is two to seven. Every 5-7 days is preferred, but it is most preferred that anti-progestagen be administered only one time additionally, i.e. in total twice a month. Particularly in the embodiments in which anti-progestagen is administered more than one time additionally, it is preferred to administer it simultaneously with progestagen, i.e. the anti-progestagen does not
25 substitute the progestagen but comes in addition. It is important that the anti-progestagen is administered only one day at a row. For HRT regimens it is desired for the anti-progestogen to be dosed in as low an amount as is capable of inhibiting bleeding, without inducing menses.

30 In the method of this invention the contraceptive and/or HRT kit consists of four phases, in which the first phase is a single dosage unit comprising an anti-progestogen and optionally a progestogen, the second phase containing progestogen, estrogen or a

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mixture thereof, the third phase comprising an anti-progestogen and optionally a progestogen, and the fourth phase containing progestogen, estrogen or a mixture thereof.

- 5 Preferably the dosage of the anti-progestogen in the third and optional further phases is lower than the dosage of the anti-progestogen in the first phase. More preferably the first phase consists of 10 to 150 mg of Org 31710, and most preferably 25 mg of Org 31710, and the third phase (and any optional subsequent phase) consists of 0.5 to 25 mg, more preferably of 2.5 to 12.5 mg, and even more preferably of 5 mg of Org
- 10 31710. In the case of a more than four-phase regimen involving more than two times administration of anti-progestagen, the first phase dosage will generally be the same as above, but it is possible to further decrease the dosage in the subsequent phases.

- For HRT regimens dosage units comprising the anti-progestogen units as above and
- 15 units comprising an estrogen, progestogen or mixtures thereof are envisaged. Estrogens which can be used include 17 β -estradiol and ethinyl estradiol. Mestranol (17- α -ethinyl estradiol 3-methylether) and conjugated estrogens are also useful estrogens. Suitable amounts of ethinyl estradiol per dosage unit are between 0.005 and 0.1 mg. Of course amounts having equivalent activity of other estrogens can also be
- 20 used. As an approximation, 1 mg of 17 β -estradiol is equivalent in estrogenic activity to 0.015 mg of ethinyl estradiol and 0.030 mg of mestranol.

- The progestogen and anti-progestogen are incorporated into dosage units for oral administration. The term "dosage unit" generally refers to physically discrete units
- 25 suitable as unitary dosages for humans, each containing a predetermined quantity of active material calculated to produce the desired effect, for instance tablets, pills, powders, suppositories, capsules and the like.

- Methods and compositions for making such dosage units are well-known to those skilled in the art. For example, conventional techniques for making tablets and pills,
- 30 containing active ingredients, are 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).

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For making dosage units, e.g. tablets, the use of conventional additives, e.g. fillers, colorants, polymeric binders and the like is contemplated. In general any pharmaceutically acceptable additive which does not interfere with the function of the active compounds can be used in the one or more of the compositions.

- 5 Suitable carriers with which the compositions can be administered include lactose, starch, cellulose derivatives and the like used in suitable amounts. Lactose is a preferred carrier. Mixtures of carriers can also be used.

- 10 A process of manufacturing the kit of the invention comprises mixing predetermined quantities of progestogen (for instance desogestrel, 3-ketodesogestrel, or mixtures thereof) or anti-progestogen (for instance Org 31710) with predetermined quantities of excipients and converting the mixture into dosage units containing progestogen or anti-progestogen.

- 15 For HRT regimens unit dosages may be obtained by mixing predetermined quantities of progestogen and estrogen.

Preferred kits contain a total of 20 to 32 of said daily sequential dosage units.

Converting the mixture into dosage units generally involves moulding the mixture into a tablet, filling a capsule with a dried mixture, or filling a capsule with a wet mixture.

- 20 A preferred process of manufacturing the pharmaceutical product according to the invention involves incorporating the desired dosages of contraceptive steroid (for example desogestrel, 3-ketodesogestrel, or mixtures thereof) into tablets by techniques such as wet granulation tableting techniques. The package containing the dosage units will contain between 7 and 180, preferably 28, dosage units.

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While the description hereinbefore refers to daily dosage units making up the anticonceptive or HRT kit, the method of treatment according to the invention extends to any other suitable form of administration. Therefore, the invention relates to pharmaceutical preparations capable of releasing progestagen and anti-progestagen, optionally simultaneously, in accordance with the regimen described above. Thus the administration in four or more phases of anti-progestagen and progestagen can be effectuated not only through tablets, but also by means of an implant system, a vaginal ring, injectable systems, transdermal systems, or by any combination thereof

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(particularly: the progestagen administered as a tablet, the anti-progestagen in the form of a non-oral system such as an implant).

The invention is further explained by the following illustrative examples.

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Example I

The following coated tablets intended for once daily administration were made:

Composition (per tablet):

10

Tablet I

<u>Compound</u>	<u>Amount (mg/tablet)</u>
desogestrel	0.075
corn starch	6.500
15 povidone	1.950
stearic acid	0.650
colloidal silicone dioxide	0.650
dl- α -tocopherol	0.080
lactose	qsad 65.000

20

Coating layer: (filmcoat-dry)

<u>Compound</u>	<u>Amount (mg/tablet)</u>
hydroxypropylmethylcellulose	0.75
25 polyethylene glycol 400	0.15
titanium dioxide	0.1125
talc	0.1875

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Tablet II

	<u>Compound</u>	<u>Amount (mg/tablet)</u>
	Org 31710	25
5	corn starch	6.500
	povidone	1.950
	stearic acid	0.650
	colloidal silicone dioxide	0.650
	dl- α -tocopherol	0.080
10	lactose	qsad 65.000

The same coating layer as for tablet I was used.

Tablet III

15	<u>Compound</u>	<u>Amount (mg/tablet)</u>
	Org 31710	5
	corn starch	6.500
	povidone	1.950
20	stearic acid	0.650
	colloidal silicone dioxide	0.650
	dl- α -tocopherol	0.080
	lactose	qsad 65.000

25 The same coating layer as for tablet I was used.

The tablets were packed in push-through packs as follows:

1 Tablet II

13 Tablets I

30 1 Tablet III

13 Tablets I

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The push through packs are placed in folding cartons, which are additionally sealed in aluminum sachets.

5 **Example II**

The tablets of Example I, along with similar tablets containing 0.030 and 0.050 mg of desogestrel were tested in healthy female volunteers in a non-public, double-blind randomized study. Ovulation was completely inhibited with the tablets of Example I.

10 Furthermore, the use of the tablets of Example I also had a low percentage of bleeding and spotting days in comparison to conventional regimens of desogestrel.

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Claims

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1. A contraceptive and/or HRT (hormone replacement therapy) kit comprising sequential daily dosage units each containing as the sole contraceptively effective ingredient a progestogen, or as effective ingredient for HRT a progestogen with or without an estrogen or an estrogen only, and further two dosage units comprising an anti-progestogen.
2. The contraceptive and/or HRT kit of claim 1 wherein said kit contains a total of 20 to 32 dosage units.
3. The contraceptive and/or HRT kit of claim 1 or 2 consisting of four phases, in which the first phase is a single dosage unit containing an anti-progestogen and optionally a progestogen, the second phase containing progestogen, estrogen or a mixture thereof, the third phase containing an anti-progestogen and optionally a progestogen, and the fourth phase containing progestogen, estrogen or a mixture thereof.
4. The contraceptive and/or HRT kit of claim 1 consisting of four phases, in which the first phase is a single dosage unit containing an anti-progestogen and optionally a progestogen, the second phase consists of 9-15 dosage units containing progestogen, estrogen or a mixture thereof, the third phase is a single dosage unit containing an anti-progestogen and optionally a progestogen, and the fourth phase consists of 9-15 dosage units containing progestogen, estrogen or a mixture thereof.
5. A contraceptive and/or HRT kit 1 consisting of four to eight phases in which the odd-numbered phases all comprise a single dosage unit containing an anti-progestogen and optionally a progestogen and the even-numbered phases all consist of 8-15 dosage units containing progestogen, estrogen or a mixture thereof.

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6. The contraceptive and/or HRT kit of claim 3, 4 or 5, further comprising placebo dosage units.
- 5 7. The contraceptive and/or HRT kit of any one of claims 3 to 6, wherein the dosage of the anti-progestogen in the third phase and, if present, subsequent phases, is lower than the dosage of the anti-progestogen in the first phase.
- 10 8. The contraceptive and/or HRT kit of any one of claims 1-7, wherein the progestogen is desogestrel present in a quantity of 75 µg per dosage unit and the antiprogestogen is Org 31710 present in a quantity of 25 mg in the first phase and in a quantity of 2.5 to 12.5 mg in the third and subsequent phases.
- 15 9. The use of daily dosage units consisting essentially a progestogen, and of an anti-progestogen, in the preparation of a drug delivery system, said drug delivery system characterized by consisting of daily dosage units containing only a progestogenic compound as therapeutically effective ingredient and two to seven dosage units comprising anti-progestogen, one of which is administered at the beginning, and the other or others divided regularly throughout the cycle.
- 20 10. The use of oral daily dosage units consisting essentially of an estrogen and a progestogen, and of an anti-progestogen, in the preparation of a drug delivery system, said drug delivery system characterized by consisting of daily dosage units containing progestogen and/or estrogen as therapeutically effective ingredient and two to seven dosage units comprising an anti-progestogen, one of which is administered at the beginning and the other or others divided regularly throughout the cycle.
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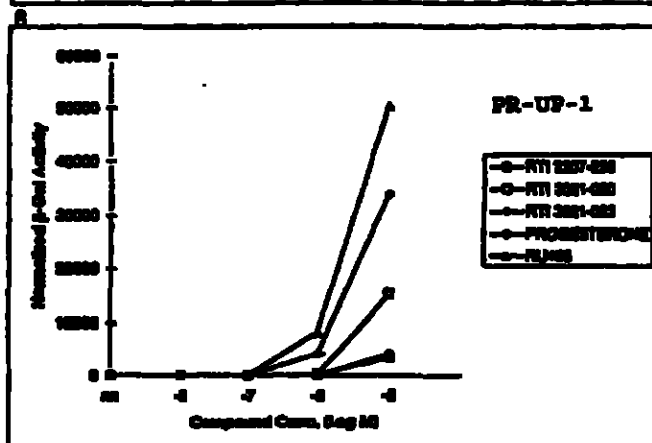
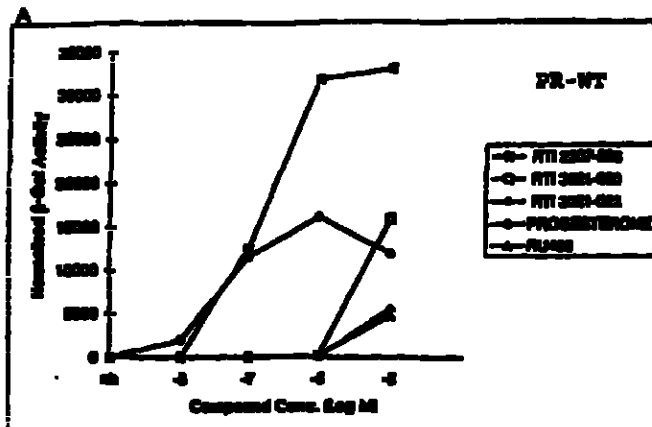
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(71) Applicant: DUKE UNIVERSITY [US/US]; Office of Science and Technology, 230 North Building, Research Drive, Box 90083, Durham, NC 27708-0083 (US).			
(72) Inventors: McDONNELL, Donald, P.; 113 North Haven Drive, Chapel Hill, NC 27516 (US). WAGNER, Brandee, L.; Apartment 3, 150 Beaconsfield Road, Brookline, MA 02146 (US).			
(74) Agents: CHEN, Anthony, C. et al.; Lyon & Lyon LLP, Suite 4700, 633 West Fifth Street, Los Angeles, CA 90071-2066 (US).			

(54) Title: MIXED ANTAGONISTS OF THE PROGESTERONE RECEPTOR AND ASSAYS THEREFOR

(57) Abstract

A third class of PR-ligand (i.e. mixed agonist) is identified which induces a progesterone receptor conformation distinct from that induced by a PR agonist or antagonist. PR mixed agonists exhibit partial agonist activity which is influenced by cell context. These compounds provide useful pharmacological profiles for treating progesterone related diseases and/or conditions. Assays are provided to screen for PR mixed agonists. Molecular designs are provided to convert a PR antagonist to a PR mixed agonist.



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MIXED ANTAGONISTS OF THE PROGESTERONE RECEPTOR AND ASSAYS THEREFOR**FIELD OF THE INVENTION**

This invention relates to agonists and antagonists for progesterone receptors and assays for screening for agonists and antagonists active at progesterone receptors.

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BACKGROUND OF THE INVENTION

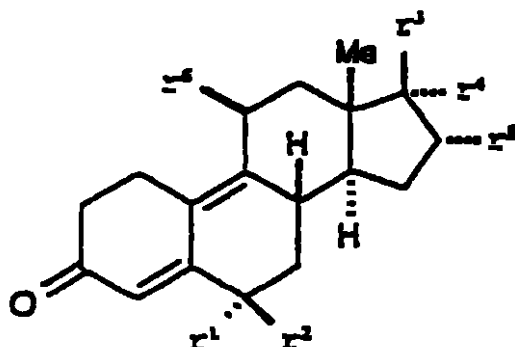
The steroid hormone progesterone is involved in the regulation of growth and development of mammary gland and uterus. Synthetic progestins and antiprogestins have been used or are in human clinical trials in treatment of endometrial and breast cancer, as combination oral contraceptive agents, and as adjuncts to estrogen in hormonal replacement therapy.

Produced in the ovaries, and passed into the blood stream, progesterone manifests biological activity primarily in those cells which express intracellular progesterone receptors (PRs). Upon binding to their hormonal ligands, the activated progesterone receptors bind with high affinity to specific DNA binding sites and activate transcription of the cis-linked genes. PR is a member of the steroid hormone receptor superfamily.

A typical steroid hormone receptor can be divided into six domains, A, B, C, D, E and F as indicated in Figure 7. The function of each domain is indicated by solid lines. The N-terminal A/B domain contains a transactivation function. The C region is responsible for DNA binding and receptor dimerization. The D region is a hinge region which allows the

"novel" is meant that the mixed agonist compound or composition is not known or used before this invention.

In a preferred embodiment, the mixed agonist is of the formula:



where the r groups are independently:

r^1 is H, CF_3 , CH_3 ,

r^2 is H, CF_3 , CH_3 ,

r^3 is $r^3C=O$, or r^3

r^4 is H, F, Cl, Br, I, NO_2 , CO_2H , CO_2r^6 , CHO, CN, CF_3 , CH_2OH , optionally substituted C1-C6 alkyl or perfluoroalkyl, optionally substituted allyl, arylmethyl, aryl, heteroaryl, alkynyl or alkenyl

r^5 is H, F, Cl, Br, I, NO_2 , CO_2H , CO_2r^6 , CHO, CN, CF_3 , CH_2OH , optionally substituted C1-C6 alkyl or perfluoroalkyl, optionally substituted allyl, arylmethyl, aryl, heteroaryl, heteroarylmethyl, alkynyl or alkenyl

r^6 is optionally substituted C1-C12 alkyl or perfluoroalkyl, optionally substituted allyl, arylmethyl, aryl, heteroaryl, heteroarylmethyl, alkynyl or alkenyl, including but not limited to 4-acetylphenyl, 4-methoxyphenyl, 4-fluorophenyl, 4-cyanophenyl

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said host, endometrial cancer, breast cancer, fibroids, and brain meningiomas. The composition of this invention may also be used as contraceptive to prevent unwanted pregnancy.

By "pharmaceutically effective amount" is meant an amount of a pharmaceutical compound or composition having a therapeutically relevant effect on a progesterone related disease or pathological condition. A therapeutically relevant effect relieves to some extent one or more symptoms of endometriosis, uterine proliferation caused by administration of estrogen to said host, endometrial cancer, breast cancer, fibroids, and brain meningiomas, or other disorders in a patient or returns to normal either partially or completely one or more physiological or biochemical parameters associated with or causative of the diseases or pathological conditions.

Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A and 1B are graphs showing normalized β -Gal activity in *Saccharomyces cerevisiae* transformed with an expression vector encoding either PR-WT(YEphPR) (Fig. 1A) or PR-UP-1(YEphPR-UP-1) (Fig. 1B) and a vector containing PRE-CYC1- β -galactosidase reporter gene.

Transformed yeast cells were grown to exponential growth phase, whereupon ligands were added as indicated. Following a 4 hr incubation, the cells were harvested and ligand induced transcriptional activity was measured. The data presented are from a representative experiment which has

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phosphatase activities in this cell line following administration of the test compound alone or in the presence of progesterone.

RTI 2207-226, which is predicted from the yeast data to be an agonist, induces alkaline phosphatase activity in a manner similar to progesterone (Figure 2A) and does not antagonize progesterone induced transcriptional activity (Figure 2B).

RTI 3021-023, which is predicted from the yeast data to be an antagonist, functions as an antagonist as shown by its ability to inhibit progesterone induced alkaline phosphatase activity (Figure 2B).

RTI 3021-020, which is predicted from the yeast data to belong to a third class of PR-ligand, functions as a partial agonist (Figure 2A) and antagonizes the alkaline phosphatase activity induced by progesterone to a level equivalent to the maximal agonist activity of RTI 3021-020 by itself (Figure 2B).

These results confirm that PR-ligands can be separated into at least three distinct classes and support the hypothesis that the biological activity of a compound can be predicted based upon its ability to interact with specific regions within the LBD of PR.

Example 3: Mixed agonist induces a unique conformation change with PR.

Applicant turned next to address possible mechanism(s) responsible for the mixed agonist activity RTI 3021-020. One explanation was that RTI 3021-020 may

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Uses of Mixed Agonists

The steroid hormone progesterone is a key modulator of the cellular processes required for the development and maintenance of reproductive function. Produced primarily by ovarian granulosa cells, it mediates its biological activity throughout the body by interacting with specific high affinity nuclear receptors located within target cell nuclei. Actions outside of the reproductive system have been implied by the localization of specific receptors for progesterone in "n n endocrine" targets such as bone. These progesterone receptors are latent transcription factors which upon binding progesterone are capable of interacting with specific recognition sequences within target gene promoters. The consequence of these interactions are determined by the cell and promoter context of the DNA bound receptor.

From a clinical perspective regulation of progesterone receptor transcriptional activity is of extreme importance. There exists several pharmaceutical agents which are used in the clinic to mimic (agonists) or oppose (antagonists) the actions of progesterone. Below is a description of the current use of these compounds, their side effects and the advantages of a mixed agonist.

Oral contraceptives

Progesterone agonist formulations have been used as single agents (Depo-provera or Norplant), or in combination with estrogens, to regulate ovulation and implantation. In addition to fertility control, these formulations are also used to treat abnormalities in the periodicity of the

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menstrual cycle. Currently these drugs are delivered as pills, implants, injectables or as topicals (patch). Agonist containing vaginal rings and intrauterine devices are also being considered. Unfortunately, because the known progesterone agonists do not display any tissue selectivity, they activate the progesterone receptor in tissues other than those required to regulate reproductive function. The lack of selectivity may be responsible for weight gain, dysfunctional bleeding and mood disorders associated with current progestins. A mixed agonist which displays tissue (or processes) specific activities may be useful for these applications.

Hormone replacement therapy

One of the problems associates with estrogen replacement therapy is that in post-menopausal women there is insufficient progesterone produced to counteract the proliferative activities of estrogen in the uterus. This unopposed action of estrogen is a risk factor for endometrial cancer. Consequently, it is becoming increasingly popular for physicians to use formulations containing progesterone for this activity. However, as the current progestins are not tissue selective there is concern that these agents in addition to counteracting the actions of estrogen in the endometrium (a desired activity) may also have the undesired side effect of reducing the efficacy of estrogen in the cardiovascular system, bone and in the central nervous system. A mixed agonist may provide the desired selectivity.

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Progesterone receptor antagonists

Although progesterone agonists have been used clinically for quite some time, it is only in the last few years that progesterone receptor antagonists have been used. Antiprogestins (like RU486) bind to the receptor and oppose the natural actions of progesterone. These compounds have been shown to be effective in the treatment of uterine fibroids, endometriosis, breast cancer, and brain meningiomas. In addition to these activities, antiprogestins have also been shown to be effective as contraceptives, missed menses inducers, and as agents to facilitate termination of early stage pregnancies. For acute applications it appears as if the current antiprogestins are very good. However, for chronic treatments the current generation of antiprogestins have selectivity problems. Not only do they manifest antiprogestational activity in all tissues where a progesterone receptor is present but it has now been observed that these compounds bind also to the receptor for glucocorticoids. Consequently, there is clinical demand for a new class of PR-antagonists which would exhibit more selectivity. The mixed agonists may provide these benefits.

Materials and Methods

Yeast Transformation and β -Galactosidase Assays.

All assays were performed in the yeast strain YPH500 (Mat α ura 3-25, lys 3-810_o, ade 2-101_o, trp 1-A63, his 3-A200, leu 2-A1) (9). Yeast cell transformations were performed using a modified lithium acetate protocol (10). Specifically YPH500 was transformed with the β -galactosidase reporter

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centration. receptor expression levels were normalized to protein and calculated as pmoles of steroid binding/mg protein. Values for competitive binding of unlabeled ligands are averages of duplicate determinations and were calculated as a % of total [³H]RU486 binding; set as 100% in the absence of competition. Non specific binding was determined by parallel incubations of mock transfected COS-1 cells and was between 10-15% of the total.

Pharmaceutical Formulations and Modes of Administration

10 The particular compound that affects the disorders or conditions of interest can be administered to a patient either by themselves, or in pharmaceutical compositions where it is mixed with suitable carriers or excipient(s). In treating a patient exhibiting a disorder of interest, a therapeutically effective amount of a agent or agents such as these is administered. A therapeutically effective dose refers to that amount of the compound that results in amelioration of symptoms or a prolongation of survival in a patient.

20 The compounds also can be prepared as pharmaceutically acceptable salts. Examples of pharmaceutically acceptable salts include acid addition salts such as those containing hydrochloride, sulfate, phosphate, sulfamate, acetate, citrate, lactate, tartrate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-t luenesulfonate, cyclohexylsulfamate and quinate. (See e.g., PCT/US92/03736). Such salts can be derived using acids such as hydrochloric acid, sulfuric acid, phosphoric acid, sulfamic

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The present invention also encompasses pharmaceutical compositions prepared for storage and subsequent administration, which have a pharmaceutically effective amount of the products disclosed above in a pharmaceutically acceptable carrier or diluent. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical art, and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co. (A.R. Gennaro edit. 1985). Preservatives, stabilizers, dyes and even flavoring agents may be provided in the pharmaceutical composition. For example, sodium benzoate, sorbic acid and esters of p-hydroxybenzoic acid may be added as preservatives. Id. at 1449. In addition, antioxidants and suspending agents may be used. Id.

The compositions of the present invention may be formulated and used as tablets, capsules or elixirs for oral administration; suppositories for rectal administration; sterile solutions, suspensions for injectable administration; and the like. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. Suitable excipients are, for example, water, saline, dextrose, mannitol, lactose, lecithin, albumin, sodium glutamate, cysteine hydrochloride, and the like. In addition, if desired, the injectable pharmaceutical compositions may contain minor amounts of nontoxic auxiliary substances, such as wetting agents, pH buffering agents, and the like. If desired, absorption enhancing preparations (e.g., liposomes) may be utilized.

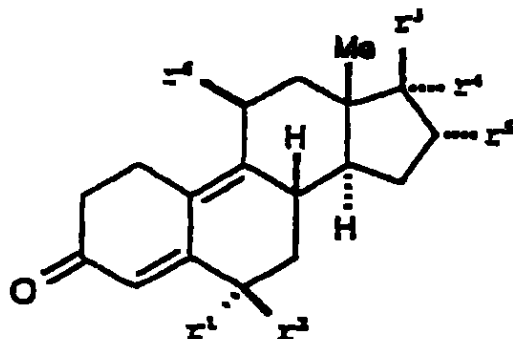
WHAT IS CLAIMED IS:

1. A novel mixed agonist of progesterone receptor which is capable of interacting with and binding both the agonist pocket of progesterone receptor and the antagonist pocket of progesterone receptor.

2. The novel mixed agonist of claim 1 which is capable of binding and activating the transcription activation activity of both PR-WT and PR-UP-1.

3. The novel mixed agonist of claim 1 which is capable of binding and activating the transcription activation activity of both PR-722 and PR-UP-1.

4. The novel mixed agonist of claim 1 of the formula



wherein R1 = -H or -CH₃; R2 = -OH or -COCH₃; R3 = -CH₂N₃, -CH₂OCH₃, -OAc or -H; and R4 = -C_nH_{2n+1}; n is an integer greater than 2.

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18. The method of claim 14, wherein both said first cell and said second cell are mammalian cells.

19. The method of claim 11 by detecting a compound which is both capable of competing with progesterone to bind said agonist pocket and capable of competing with RU486 to bind said antagonist pocket.

20. The method of claim 11 by detecting a compound which binds PR-WT and induces PR-WT into a conformation which is different from that induced by progesterone or RU486.

21. A novel compound identified by a method of claims 11-20 as a mixed agonist of progesterone receptor.

22. Method for converting an antagonist of progesterone receptor which has a steroid backbone into a mixed agonist of progesterone receptor, comprising the step of adding an alkyl group to the 16 α carbon position of said steroid backbone of said antagonist.

23. Method for treating a host with a progesterone related disease or pathological condition or preventing said host from said disease or pathological condition by administering to said host a pharmaceutically effective amount of a mixed agonist of progesterone receptor.

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24. The method of claim 23, wherein said mixed agonist is a chemical compound capable of binding and activating the transcription activation activity of both PR-UP-1 and PR-722.

25. The method of claim 23, wherein said mixed agonist is a chemical compound capable of binding and activating the transcription activation activity of both PR-UP-1 and PR-WT.

26. The method of claim 23, wherein said mixed agonist is selected from the group consisting of RTI 3021-020, 3021-021, 3021-022, and pharmaceutically acceptable salts thereof.

27. The method of claim 23, wherein said progesterone related disease or pathological condition is selected from the group consisting of uterine proliferation caused by administration of estrogen to said host, endometriosis, endometrial cancer, breast cancer, fibroids, and brain meningiomas.

28. The method of claim 23, wherein said mixed agonist is a compound of claims 1-9.

29. Method for preventing unwanted pregnancy by administering to a host a pharmaceutically effective amount of a mixed agonist of progesterone receptor.

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30. The method of claim 29, wherein said mixed agonist is a chemical compound capable of binding and activating the transcription activation activity of both PR-UP-1 and PR-722.

5 31. The method of claim 29, wherein said mixed agonist is a chemical compound capable of binding and activating the transcription activation activity of both PR-UP-1 and PR-WT.

10 32. The method of claim 29, wherein said mixed agonist is selected from the group consisting of RTI 3021-020, 3021-021, 3021-022, and pharmaceutically acceptable salts thereof.

15 33. The method of claim 29, wherein said mixed agonist is a compound of claims 1-9.

34. A pharmaceutical composition adapted for the treatment of a host having a progesterone related disease or pathological condition, comprising (a) a pharmaceutically effective amount of a mixed agonist of progesterone receptor; and (b) a pharmaceutically acceptable carrier.

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25 35. The pharmaceutical composition of claim 34, wherein said mixed agonist is a chemical compound capable of binding and activating the transcription activation activity of both PR-UP-1 and PR-722.